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**THE CONTRIBUTION OF REORGANISED MOTOR
PATHWAYS TO RECOVERY OF ARM AND HAND FUNCTION
AFTER STROKE.**

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MSc. Rehabilitation Studies, Dip. COT.

**Submitted for the degree of
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THE CONTRIBUTION OF REORGANISED MOTOR PATHWAYS TO RECOVERY OF ARM AND HAND FUNCTION AFTER STROKE.

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ABSTRACT

Stroke often disrupts the descending motor pathways controlling the upper limb with severe consequences for patients' hand function. Although some recover they are often slow and clumsy when using the affected hand. The mechanism underlying recovery is an unsettled question. Transcranial magnetic stimulation (TMS) was used to determine the changes in the connectivity and function of the corticospinal tract (CST) that are associated with improved motor performance in the recovering arm and hand. The study comprised four parts:

1. Task dependency of responses to TMS in recovered stroke patients.

Eight patients, who had recovered some degree of hand function were tested for task dependence of short-latency EMG responses to TMS. Normal subjects were also tested.

2. Longitudinal investigation of recovery of voluntary movement of arm and hand after stroke.

The relationship between the recovery of hand and arm function in a group of acute stroke patients (n=21) and the presence of short latency contralateral and ipsilateral EMG responses to TMS in four different upper limb muscles was investigated.

3. Ipsilateral responses in normal subjects.

The results of the longitudinal study prompted further investigation of the presence of ipsilateral responses in proximal and distal muscles in fifteen normal subjects.

4. The contribution of CS input to production of force in proximal and distal upper limb muscles.

Because patients did not always have responses to TMS in recovered proximal muscles, two further studies were carried out to clarify the contribution of CS input to production of force in proximal and distal upper limb muscles. First, the effect of voluntary contraction on response amplitudes in deltoid, biceps and 1DI were compared. Second, the effect of increasing stimulus intensity on recruitment of low threshold motor units was assessed for deltoid and 1DI. In addition the change in response amplitude with increasing voluntary activity in the affected and unaffected shoulder muscles of three patients were compared.

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ABBREVIATIONS

1DI	first dorsal interosseous
A-D	analogue to digital
AbDM	abductor digiti minimi
AbPB	abductor pollicis brevis,
CED	Cambridge Electronic design
CM	corticomotoneuronal
CMCT	central motor conduction times
CNS	central nervous system
CS	corticospinal
CST	corticospinal tract
CT scan	computerised tomography scan
DC	double cone coil
DTR	data tape recorder
EDC	extensor digitorum communis
EMG	electromyograph
EPSPs	excitatory post synaptic potentials
group A patients	rapid recovery group
group B patients	slow and incomplete recovery group
H-reflexes	Hoffman reflexes
HRP	horse radish peroxidase
IP	interphalangeal
LTP	long term potentiation
MCP	metacarpophalangeal
MRC muscle tests	Medical Research Council muscle tests
MRI	magnetic resonance imaging
MU-TA	motor unit-triggered average
MVC	maximum voluntary contraction
P	probability
PC	personal computer
PET	positron emission tomography
PSTHs	peristimulus time histograms
rCBF	regional cerebral blood flow
RMS	root mean square
SMA	supplementary motor area
SMU, #1 AND #2	first and second single motor unit
STA	spike-triggered averaging
TES	transcranial electrical stimulation
TMS	transcranial magnetic stimulation
V+3	3 cm lateral to vertex
V+6	6 cm lateral to vertex

Response categories for longitudinal study

1. No response to TMS, no voluntary EMG activity.
2. Response to TMS, no voluntary EMG activity.
3. No response to TMS, voluntary EMG activity.
4. Response to TMS and voluntary EMG activity.

CHAPTER ONE

INTRODUCTION AND BACKGROUND.

1.1 Introduction.

"Dear Sir

It has pleased God by a paralytick stroke in the night to deprive me of my speech.", wrote Samuel Johnson in 1783. At a stroke the ease with which we speak, walk, dress, eat, shake hands, work and play can be gone. Stroke is caused by a breakdown in the blood supply within the brain. It is defined by the World Health Organisation as "rapidly developed clinical signs of focal (or global) disturbance of cerebral function, lasting more than twenty four hours or leading to death, with no apparent cause other than of vascular origin" (Aho, Harmsen, Hatano, Marquardsen et al., 1980). Samuel Johnson's stroke primarily affected his speech and fortunately he was able to write notes to send for his doctors and also to tell his friends. These extracts from two of his letters describe how he was treated.

Thursday 19th June 1783.

"I suppose you may wish to know how my disease is treated by the physitians. They put a blister upon my back and two from my ear to my throat on one side. The blister on the back has done little, and those on the throat have not risen.....They likewise give me salt of hartshorn, which I take with no great confidence, but I am satisfied that what can be done is done for me."

Friday 20th June 1783.

"I have now healing application to the cheeks and have my head covered with one formidable diffusion of cantharides¹, from which Dr Heberden assures me that experience promises great effects. He told me likewise that my utterance has been improved since Yesterday, of which however I was less certain. Though doubtless they who see me at interval can best judge."

(The Letters of Samuel Johnson, 1783-1784, collected and edited by RW Chapman, 1952).

¹ Cantharides are spanish flies that were used to raise blisters (Shorter Oxford English Dictionary).

Johnson's treatment was based on the premise that the disorder stemmed from malfunctioning of the body fluids, or humours, at a particular site. The blisters may have been applied to his back to draw the offending humours away from the neck; and on his cheek to bring them to the surface (Wiltshire, 1991). In the light of today's understanding it appears that the eighteenth century doctors may have been unwittingly close to identifying a circulatory problem within the carotid artery as the cause of Johnson's stroke. It is common place now for stroke patients to receive medication to control more specifically the disordered blood circulation that may have contributed to the event. Hypertension is reduced and thromboses are prevented pharmacologically and sometimes obstructions in the carotid artery are surgically removed (Sandercock and Willems, 1992; Warlow, 1992).

It is estimated that about 99,000 people have a first ever in a life time stroke each year in England and Wales (Bamford, Sandercock, Dennis, Warlow et al., 1988). 30% are likely to die within the first month (see Wade, 1985). Those that survive, may feel that with today's medical knowledge, the circulatory problem that caused the stroke may be remedied or controlled, so that the likelihood of further strokes occurring are diminished. However treatment for the neurological consequences of stroke, which disable the majority of patients, have not advanced very much. Drugs capable of limiting the damage to ischaemic brain cells have started to become a subject for clinical trials (Major ongoing stroke trials, 1994; Whitfield and Pickard, 1994), but these have to be administered within a few hours of the onset of stroke. Even if they are found to be beneficial, these drugs are likely to be limited in their value for many patients who may not receive medical attention in time (Pulsinelli, 1992, Ginsberg and Pulsinelli, 1994). Pharmacological or other types of intervention for brain repair are not available. Today's patients often spend weeks in hospital either recovering or adapting slowly until they are able to look after themselves at home or until they can be cared for, or they are discharged, still very disabled to

nursing homes. At present, the remediation of movement, speech, perceptual and cognitive impairments are limited to the efforts of the patients themselves, their family and the various rehabilitation professionals. Many therapists base their intervention on the assumption that recovery is dependent on the ability of the central nervous system to change (Gordon, 1987; Kidd, Lawes and Musa, 1992), but there is still little understanding of what changes can and do actually take place. It is clear that many patients with irreversible destruction of brain tissue make remarkable recoveries. A notable case history is that of a college professor who after suffering a stroke gradually regained a considerable level of skill in using the affected hand and arm over a period of five years. Some time later he died of a heart attack. An autopsy revealed extensive brain damage and atrophy of the corticospinal tract which had occurred at the time of the stroke (Bach y Rita, 1980). The importance of the corticospinal tract for voluntary movement is well established, so the professor's regained movement must have been due to substantial reorganisation of the descending motor pathways. Precisely what reorganisation occurs to bring about motor recovery remains unknown. An improved grasp of the underlying mechanisms might ultimately enable the development of more effective therapy and a better outlook for stroke patients.

This study using transcranial magnetic stimulation (TMS) was undertaken to investigate the reorganisation of the descending motor pathways that takes place during recovery of arm and hand movement after stroke. TMS excites the cells of origin of the corticospinal tract and evokes electromyographic (EMG) responses in muscles on the contralateral side of the body. It is a painless and non-invasive means by which the degree of disruption to the corticospinal tract by stroke and the changes in its conduction that take place during recovery, can be assessed directly.

This chapter will account for the motor deficits that are commonly seen after stroke and explain how they relate to disruption of the corticospinal control of movement.

Some hypotheses of the mechanisms that operate to bring about successful recovery and evidence in their support will then be offered. Finally the use of TMS will be introduced as a method for investigating the relationship between hand function and corticospinal activity and thus for exploring the role of the pathway in successful recovery of voluntary upper limb movement following stroke.

1.2 Motor deficits after stroke.

More than three quarters of acute strokes are caused by occlusion of a cerebral artery producing an area of infarction. About three quarters of cerebral infarctions occur in the territory of the middle cerebral artery (Allen, Harrison and Wade, 1988). The large extent of the cortical motor areas together with the large number of long fibres that descend from them that are within the territory of the middle cerebral artery and its branches explains the common occurrence of weakness and poverty of movement after stroke. A common site of infarction is the internal capsule. Here the descending fibres pass in great number between the thalamus and basal ganglia. Ischaemia in the internal capsule can therefore lead to mass disruption of projections that connect large areas of the cortex with the motor centres in the brainstem and spinal cord and also to afferent ascending pathways which carry important information for the control of movement.

Weakness of one side of the body (hemiparesis) is the most obvious characteristic of stroke, but the weakness is not uniform on the "affected" side. Many midline body parts appear to be relatively spared, for example some facial muscles, respiratory and abdominal muscles are not so profoundly affected as those in the arm or leg (Broadbent, 1866; Walshe, 1947; Willoughby and Anderson, 1984). Even within the limbs the degree of weakness between muscles varies. Colebatch and Gandevia (1989) used specially designed isometric myographs to determine strength of different muscle groups in the upper limb of 10 stroke patients. Although the pattern of weakness was not always the

same, it was striking that in many of the patients it was the more distal hand and finger muscles which were most affected, while the proximal muscles were substantially less weak. A previous investigation of strength measured with a hand held dynamometer yielded similar results. Bohannon and Smith (1987) found wrist extensors were weaker than elbow and shoulder muscle groups.

A similar pattern of loss has been found in estimates of the number of functioning motor units in stroke patients. The health of motor units is thought to depend on the maintenance of inputs from supraspinal sources (McComas, 1973); spinal motoneurons may die if they are deprived of their normal inputs. The subsequent denervation of muscle fibres can result in very small spontaneous action potentials, known as "fibrillation potentials". Fibrillation potentials are not a major characteristic of stroke but it is interesting that in a study involving 116 patients these potentials were recorded most often in distal muscles (Goldkamp, 1967). Many of the patients were tested repeatedly and Goldkamp found that the peak incidence of fibrillation potentials was at around 4 weeks after stroke. The possibility that the potentials were due to the pressure exerted on peripheral nerves, that could result from such long periods of immobility in hemiparetic limbs, was discounted because no changes in peripheral motor conduction velocities were found.

These weakness and denervation effects on different muscle groups of the upper limb in stroke patients are consistent with the pattern of excitatory influence on the motoneurone pools from the corticospinal tract (CST). Unlike other descending motor pathways, CST fibres are distributed profusely both to motoneurons innervating distal extremity muscles and to motoneurons innervating more proximal muscles (Kuypers, 1981; see Porter and Lemon, 1993).

After stroke, recovery may take place over the following weeks and months, but the motor deficits that remain for the longest also implicate disruption of the CST. In a

most comprehensive study of recovery of 121 patients, by Twitchell, (1951), voluntary movements usually returned first proximally and then progressed to include more distal muscles. Many patients recovered some voluntary movement of the proximal joints, fewer regained finger movement. Early movements were observed first in synergy patterns; for example, shoulder flexion was accompanied by flexion of the elbow, wrist and fingers. More fractionated movements were not evident until later. Twitchell also noticed that patients often took longer to contract and to relax muscles early in recovery. Since Twitchell's classic study other authors have described movement in synergy patterns as a stage of recovery (Brunnström, 1970; Fugl-Meyer, 1975; Gowland, Torresin, Van Hullenaar and Best, 1990). The reason for appearance of synergies is not clear. They could be regarded as an effect of the loss of CS input to motoneurons; the pathway has an important function in fractionating movements. A relatively greater influence of other descending motor pathways after stroke might result in synergy bound movements (Dewald, Pope, Given, Buchanan and Rymer, 1995). Alternatively patients' synergic movement could just be a feature of biomechanics. With increased recruitment of synergists the strength to lift the weak arm is boosted. Wing, Lough, Turton, Fraser and Jenner, (1990), found that patients recovered the ability to move the elbow just as soon without the shoulder as with it, in their studies in which goal directed movements were made on low resistance arm supports. Lastly the flexor synergy problem could be compounded by altered length-tension relationships in muscles that are all too often left resting for long periods in some degree of flexion.

1.3 The Corticospinal Tract - Anatomy.

It appears that disruption to the CST may be responsible for a significant share of the motor deficit after stroke. A description of its origins, course, and connections together with a summary knowledge of its involvement in the control of different movement

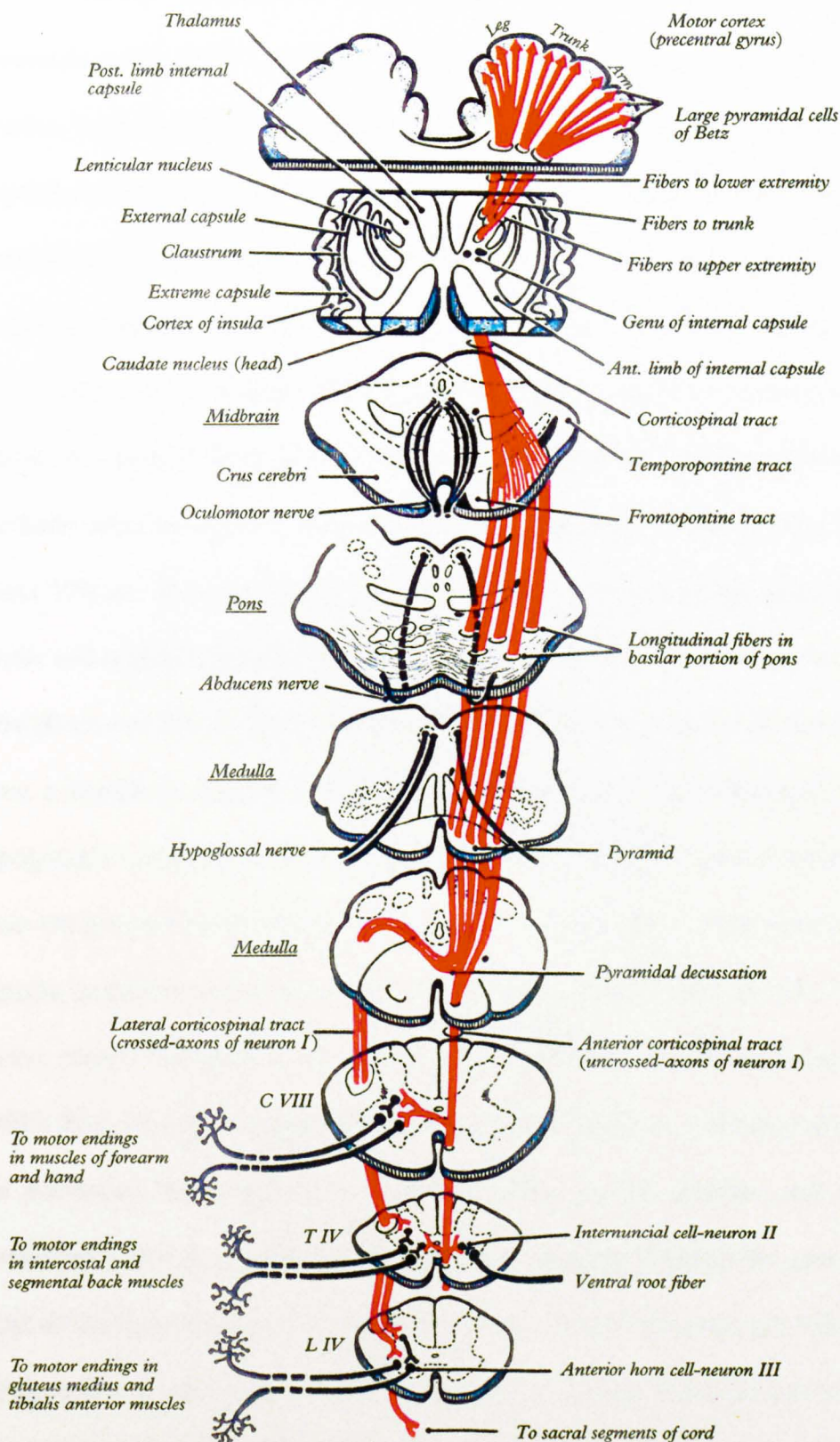


Figure 1.1 Schematic diagram of lateral and anterior corticospinal tracts. CS tracts (red), ventral and motoneurons and axons (black). Letters and numbers indicate the various levels of the spinal cord. Diagram reproduced from Grays Anatomy 1996.

parameters is useful for understanding the effects of stroke and how recovery might take place.

The CST projects directly from the cortex to the spinal cord. It is found only in mammals and is most developed in primates; and particularly in man. The wide range of actions, high degree of skill and precision that we have in using our hands is believed to depend on the dominance of cortical control in the production of movement. The CST provides the most direct link between cortex and hand and is thought to be a key factor in the development of such superior manipulatory skills (Lemon, 1993a).

Figure 1.1 illustrates the origin and course of the CST. In primates, corticospinal fibres are derived from several regions of the cerebral cortex. Anatomical labelling methods using retrograde axonal transport in experimental monkeys have estimated that about 30% are from the primary motor cortex, the rest are from premotor, supplementary motor and cingulate areas in the frontal lobe and from the postcentral gyrus of the parietal lobe (Dum and Strick, 1991). The fibres from all of the cortical motor areas converge and form a bundle to descend through the internal capsule. Up to this point at least, some topographic arrangement of the fibres from different motor areas is maintained. Axons from the primary motor cortex pass through the middle third of the posterior limb of the capsule, premotor cortex axons pass through the genu and those from the supplementary motor cortex through the anterior limb (Fries, Danek, Scheidtmann, and Hamburger, 1993). After leaving the capsule the tract proceeds through the cerebral peduncles. Below the peduncles topographical order of the fibres is lost (Nathan and Smith, 1955). Completely intermingled with each other they descend through the pons and medulla. Most of the fibres (approximately 85-90% in man), then decussate and travel on down in the dorsolateral columns of the spinal cord. These crossed fibres are known as the lateral CST. The proportion of fibres that do not decussate varies between individuals, they descend within the ventromedial part of the spinal cord and probably in the ipsilateral

lateral funiculus. The ventral fibres are known collectively as the anterior CST (Nathan, Smith and Deacon, 1990).

The lateral CS fibres terminate at all levels of the cord, but the majority do not project beyond the cervical enlargement. In man 50% are estimated to terminate in the cervical cord and 20% in the thoracic cord (Weil and Lassek, 1929; see Porter and Lemon, 1993). The motoneurons are arranged in somatotopically organised columns within the cervical segments of the spinal cord. Motoneurons that innervate distal extremities are situated in the dorso-lateral part of the ventral horn. The most dorsally located cells in the ventral horn supply the most distal muscles of the limbs and they receive the most profuse connections from the lateral CST (Kuypers, 1981). The anterior CS fibres terminate in the ventromedial part of the spinal grey matter, influencing mainly interneurons and motoneurons concerned with the axial muscles. Only crossed fibres of the CST (i.e. the lateral component) project to distal muscles (Schoen, 1964; Kuypers, 1981).

There are some differences but also some overlap within the terminal distribution of CS fibres that originate from different motor areas. The principal targets for neurones from the motor cortex are the dorsolateral part of the intermediate zone and the lateral motoneurone pools that innervate the distal muscles (Kuypers and Brinkman, 1970; Ralston and Ralston, 1985; see Porter and Lemon, 1993). Projections from more rostral parts of the motor cortex, the premotor and supplementary motor areas, appear to favour the ventromedial part of the intermediate zone, and many of these projections are bilateral (Kuypers and Brinkman, 1970; see Porter and Lemon, 1993). However a more recent labelling study has found strong distribution of CS fibres from the supplementary motor areas to the lateral motor nuclei (Rouiller, Moret, Tanne and Boussaoud, 1996).

The axons of individual CS cells may branch within the spinal grey matter to facilitate activity in a number of different hand muscles. Shinoda, Yokota and Futami,

(1981), injected horse radish peroxidase (HRP) label into axons of single CS neurones and found that single axons terminated in up to four motoneurone pools. The branches of single CS neurones allow contact with motoneurones in adjacent spinal segments to be made (Lawrence, Porter and Redman, 1985).

A feature of the CST that is peculiar to primates is a corticomotoneuronal (CM) component that makes direct monosynaptic connections with the motoneurones. As far as is known CM cells are all excitatory in influence. Their axons are probably mostly fast conducting in range, but slow fibres with direct effects have also been identified (see Porter and Lemon, 1993). In the macaque monkey most of these direct CM projections influence motoneurones that supply muscles concerned with movements of the hand and fingers, but in man there are also projections to the more medial motoneuronal cell groups concerned with axial and truncal movements (Kuypers, 1981; Schoen, 1964). CM neurones provide the cortex with direct control over the motoneurones.

1.4 Corticospinal Function.

Following the routes and connections of fibres by anatomical labelling techniques gives some idea of the influence of CS and CM cells, but recording from cells in behaving animals has provided better insights into the function of the CST. To do this fine recording electrodes are inserted into the cortex and recordings of cell discharges are made while a trained monkey performs a task that it has learned in order to obtain a food reward. Cells are identified as CS by demonstrating an antidromic response to electrical stimulation of the CST at the level of the medullary pyramid. In a typical recording experiment several hundred identified CS cells from one monkey are recorded to determine the relationship between cell activity and various movement parameters. The cells sampled are still only a tiny proportion of the total number of CS cells, but most investigators consider the sample to be representative. Most reports of such experiments

are concerned with cells in the primary motor cortex and relatively little is known about the activity or function of CS neurones in other cortical motor areas (see Humphrey and Tanji, 1991).

Because CM cells have direct input to motoneurons, their firing pattern is closely related to the EMG activity of the muscles that are specific to those motoneurons and so the relationship of CM firing with muscle activity can be examined directly. The technique used is called spike-triggered averaging (STA; Lemon 1993a). The impulses from a CM cell will produce excitatory post synaptic potentials (EPSPs) within the target motoneurone, these raise the firing probability of the motoneurone and some of the EPSPs will cause the motoneurone to discharge. If a large enough number of motoneuronal discharges occur in response to the firing of the CM cell then an increase in EMG activity, that is time locked to the discharge of the CM cell, will be evident in the accumulated EMG record from the muscle. This is known as a "post spike facilitation" and is only clear after averages triggered by many hundreds of spikes from the CM cell have been compiled.

1.4.1 Muscle field

The term "muscle field" was first used by Fetz and Cheney in 1980, to describe the group of muscles whose activity was facilitated by a single CM cell. In a number of studies, Fetz, Cheney and colleagues have used the STA technique to examine the divergent contacts to different motoneurone pools by single CM neurones. Out of one hundred CM cells that were examined during a task involving wrist flexion and extension, 67% facilitated more than two of the six flexor or extensor muscles sampled (mean 2.4 muscles per cell) (Fetz and Cheney, 1980). A slightly higher mean of three muscles per cell was found in a later investigation of 49 cells (Kasser and Cheney, 1985).

Large muscle fields appear to be less prevalent in CM neurones which facilitate intrinsic hand muscles (Lemon, Bennett, and Werner, 1991), the mean number of muscles

per cell being 1.9. Half of the most focused cells with only a single muscle in their field facilitated a thumb muscle. This part of the hand is required to be the most mobile and adaptable, so perhaps it is not surprising to find that it has such selective CM control.

Even in a simple task such as holding an object between the thumb and index finger many muscles contribute to the resulting pinch force (Maier and Hepp-Reymond, 1995) and it is possible to form the grip with varying amounts of flexion at each of the digit joints. Such fractionation of movement is only possible with highly selective facilitation. In more recent years it has become evident that cells facilitating activity in more than one muscle, do so with unequal strengths (Bennett, 1992; Bennett and Lemon, 1994). One muscle may receive strong facilitation while another will be only weakly facilitated. Recent evidence suggests that CM cells providing this type of facilitation are specifically recruited such that their pattern of influence supports the pattern of required muscle activity (Bennett and Lemon, 1996).

1.4.2 Task

Analysis of the combinations of muscles facilitated by different CM cells have in some cases reflected anatomical relationships. In another study by Fetz, Cheney and colleagues, 59% of 65 CM neurones produced pure facilitation of either flexor or extensor (i.e. agonist or antagonist). About a third of cells facilitated the agonists and produced post-spike suppression in the antagonists (30%) Cofacilitation of both flexors and extensors from a single cell was rarely found (2%), (Fetz, Cheney, Mewes and Palmer, 1989). In another example, some cells have been found to facilitate both extensor digitorum communis (EDC) and the first dorsal interosseous (1DI). Both of these muscles act to extend the interphalangeal joints of the index finger (Buys, Lemon, Mantel and Muir, 1986).

The muscle fields of other CM cells have reflected task-related synergies; such as the facilitation of 1DI and adductor pollicis brevis (the thumb adductor) which work

together in producing the precision grip (Buys et al., 1986). Activity of a target muscle is not always synonymous with increased firing in the CM cell (Bennett and Lemon, 1994). For example Muir and Lemon (1983) found that CM neurones that were particularly active during precision grip fired at lower frequencies during power grip which involves the same muscles, but in a less fractionated pattern. A task-related specificity of motor cortex output might explain the widespread representations of single muscles and considerable overlap in the cells projecting to different muscles, within the area of the motor cortex (Jackson, 1932; Donohue, Leibovic and Sanes, 1992; see Porter and Lemon 1993, Sanes, Donoghue, Thangaraj, Edelman and Warach, 1995). There have been few studies that have mapped the motor cortex according to the different roles of individual target muscles. However an investigation of two different types of activity in the wrist muscle, extensor carpi radialis, revealed distinct regions of cortical representation. Some regions of the motor cortex were found to be concerned with the muscle's role as a prime mover in extending the wrist, while others seemed concerned with the muscle's role as a fixator (Humphrey, 1986).

It seems plausible that different populations of CM cells that project to a particular muscle, are recruited according to the task in which the muscle is employed. In the intact brain, the large number of CM cells concerned may ensure a very considerable redundancy in the organisation of a particular movement. However the disruption in CST after stroke will presumably lead to a reduction in the number of CM cells projecting to intrinsic hand muscles. As a result patients may be forced to use the same population of CM cells for performance of different tasks. If the remaining population of CM cells did not recruit muscles in a manner appropriate for some tasks, this might lead to the clumsiness that patients experience when trying to use the affected hand for manipulative tasks (Brodal, 1973; Turton and Fraser, 1986).

1.4.3 Phase of movement.

Activating a muscle at the appropriate time has been recognised by several researchers as a problem for many stroke patients (Twitchell, 1951; Sahrman and Norton, 1977; Miller and Hammond, 1982). It is therefore pertinent to look at the influence of CS neurones during different phases of movement, i.e. what happens before a movement begins, at the onset and during a steady contraction? Recordings from monkeys performing wrist movements, or finger and thumb pincer grip tasks have shown that some CS neurones in motor cortex begin to change their firing rate well before the onset of movement (Evarts, 1972; Wannier, Maier and Hepp-Reymond, 1991). Some as early as 140 ms and many about 60 ms before the onset of movement (Evarts, 1972). This time is well in excess of the interval needed to allow a CS volley to reach and discharge the motoneurones.

There is a degree of inaccuracy in relating the CS output to the movement onset; a clearer picture was established by relating CS output to muscle activity using the STA technique (Fetz and Cheney, 1980). From their sample of 135 CM cells, Fetz and Cheney (1980) categorised cells according to the profile of their discharge during a wrist flexion and extension task. 28% of the cells were classified as "tonic", these were found to modulate mostly just before or after onset of EMG, but more than half (59%) were "phasic-tonic", most of these modulated their firing rate before the onset of EMG activity. Some increased their discharge rate more than 200 ms before EMG onset. Thus identified CM cells can be active well before their target muscles contract.

It is thought that the function of the early firing, phasic-tonic cells may be to prime the motoneurone, by raising its firing probability, in readiness for discharge. Perhaps stroke patients are slow to initiate movements simply because they have less cells available and therefore raising the motoneurones' excitability will take longer. Direct evidence for disruption to the CST resulting in longer reaction times and increased

latencies between EMG onset and force production has come from a study of monkeys that were trained in a reaction time task. EMG summation times were significantly longer after the tract was lesioned (Hepp-Reymond, Trouche and Weisendanger, 1974).

1.4.4 Force Production

Since weakness is one of the most striking characteristics of stroke patients' motor problems it is important to look at the relationship between changes in the firing rate of identified CS cells and force. Evarts (1968) compared the firing rates of CS cells in the wrist area of the motor cortex when trained monkeys held their wrists in flexion and extension under different load conditions. He found the cells firing rate showed a closer relationship with the force of contraction than to the position of the wrist. Since Evarts early experiments others have confirmed his findings that in monkeys as many as 30%-50% of CS cells sampled in the motor cortex modulate their firing frequency according to the force requirements of the task (see Hepp-Reymond, 1988; Cheney and Fetz, 1980; Evarts, Fromm, Kröller and Jennings, 1983; Werner, Bauswein and Fromm, 1991; Picard and Smith, 1992; Maier, Bennett, Hepp-Reymond and Lemon, 1993). The tasks employed in these experiments have essentially involved wrist or hand musculature contracting at low force levels, typically less than two newtons. However recently cells in motor cortex which increased their discharge in relation to high level isometric contractions in two elbow flexors have been identified (Fourment, Belhaj-Saïf and Maton, 1995). The latency range of post spike facilitation in both flexors was consistent with monosynaptic and disynaptic connections.

Within the populations of cells that relate to force production there are differences in firing patterns. Small CS cells are likely to be firing steadily in unloaded task conditions and increase their rate with muscle force. A limited population of larger, faster cells become active when loads are introduced (Evarts et al., 1983). Some neurones either saturate or even deactivate at high force levels (see Hepp-Reymond, 1988; Evarts et al.,

1983). Some CS neurones in the motor cortex do not simply encode muscle force but have been found to relate to the rate of change of force (Evarts et al. 1983, Hepp-Reymond and Diener, 1983). These would probably be active in controlling the speed of movement and its onset.

1.4.5 Movement of the ipsilateral limb.

In several monkey studies, cells in the hand and arm area of motor cortex that discharge in relation to movements of the ipsilateral upper limb have been identified (Evarts, 1967; Lemon, Hanby and Porter, 1976; Wannier, Toeltl, Hepp-Reymond, 1986; Tanji, Okano and Sato, 1988). The number of cells found to relate to ipsilateral movement only have been very small, but 4% - 8% have been found to relate to ipsilateral and bilateral limb movements. However a considerably higher proportion of cells relating to ipsilateral and bilateral finger movements have been identified from a particular area of motor cortex that lies between the digit and face representations (68%; Aizawa, Mushiake, Inase and Tanji, 1990). This proportion is more comparable with the percentages obtained from premotor and supplementary motor areas (Tanji et al., 1988). Bilateral CS projections are more prevalent from these areas and their role in bimanual tasks is well established (Kuypers and Brinkman, 1970; Brinkman, 1981).

In an attempt to determine what proportion of motor cortex neurones with activity related to the ipsilateral limb were CS, Matsunami and Humada (1981) found only 2/80 (2.5%) CS cells, while 11/105 (10.5%) non-CS cells that related to ipsilateral movements were identified. It is worth noting that most of the CS and non-CS cells that increased their discharge during ipsilateral and bilateral movements were related to arm movements, or to arm and hand movements, rather than to finger movements only (Matsunami and Humada 1981).

Single neurones that are associated with ipsilateral finger movements have also been found in the hand area of the motor cortex of conscious patients undergoing surgery

for focal epilepsy (Goldring and Ratcheson, 1972). More recently functional brain imaging in healthy subjects has shown increases in cortical activity in the ipsilateral motor cortex during shoulder (Colebatch, Deiber, Passingham, Friston and Frackowiak, 1991), and hand movements (Kim, Ashe, Hendrich, Ellermann et al., 1993; Kim, Ashe, Georgopoulos, Merkle et al., 1993; Kawashima, Yamada, Kinomura, Yamaguchi et al., 1993; Kawashima, Roland and O'Sullivan, 1994). At present it is not possible to distinguish CS cell activity using brain imaging techniques. The areas highlighted in the scans may have represented increased metabolic activity in cortico-cortical cells.

The role of activity in the motor cortex related to ipsilateral limb movement is unknown. It is possible that activity associated with proximal arm movements may have a role in postural control. Alternatively it may represent an inhibitory influence on the ipsilateral motoneurons when the contralateral hand is moving. Stroke patients have been shown to be a little slower than normal when using the hand ipsilateral to the damaged hemisphere (Jebson, Griffith, Long, 1971). Further investigation has demonstrated that this minor deficit is evident when making goal directed movements of the whole arm, rather than when simply making tapping movements with the hand, while the arm is supported (Baker, Walker and Baskett, 1989). It is not clear whether such slowing in performance is due to reduced drive from the motor cortex to ipsilateral proximal muscles, or whether the problems are related to impairments in processing sensory information.

1.5 Other descending motor pathways.

One could conclude that disruption to the CST can fully explain both the distribution of weakness and the poverty of movement experienced by stroke patients, but it would be imprudent not to consider the possible contribution of other descending pathways that are under the influence of the cerebral cortex. Most strokes will inevitably involve other systems as well as the CST (Warabi, Miyasaka, Inoue, and Nakamura,

1987). It is possible to estimate the amount of degeneration in the fibres descending from the cortex at the level of the cerebral peduncle and correlate it with recovery of function. Warabi, Inoue, Noda and Murakami (1990) have done this using CT imaging. They found that in all patients whose peduncles were reduced to less than 60% of the normal size, recovery of reach and grasp and independent finger movements was incomplete. Of the approximately 20 million fibres making up each of the cerebral peduncles, only about 5% are CS. The bulk of the remainder are cortico-pontine (Tomasch, 1969). This suggests that systems other than the CST have some influence over arm and hand function.

The cerebral cortex can influence the spinal cord indirectly via motor pathways which originate from the brainstem. Kuypers (1981) classified the descending motor pathways into two groups: medial and lateral pathways. The classification was based on the distribution of their terminals within the spinal cord. The vestibulospinal, the reticulospinal and the tectospinal tracts descend in the ipsilateral ventral columns of the spinal cord. Along their way they give off a considerable number of axon collaterals and terminate predominantly on interneurons and long propriospinal neurones in the ventromedial part of the intermediate zone. In contrast to the CST some of these pathways terminate bilaterally and they have influence over axial and proximal muscle groups. These tracts are known collectively as the medial pathways.

Lesion studies in monkeys have suggested that the medial brainstem pathways are concerned mainly with orienting movements of the head and body, postural control and with synergistic movements of the body and limbs (Lawrence and Kuypers, 1968b).

The reticulospinal tracts arise from the reticular formation of the pons and medulla; and terminate by making both excitatory and inhibitory connections with spinal interneurons and long propriospinal neurones. So these pathways are particularly well placed for the modulation of spinal reflexes and for influencing movement over many spinal segments. They may be important for making postural adjustments (Gahery and

Massion, 1981) and synergic movements of the limbs. Projections to these reticulospinal systems come from the premotor cortex and more rostral areas of the motor cortex (Kuypers, 1987). These corticoreticular projections are susceptible to damage by stroke and may account for proximal weakness that is observed in some patients (Freund, 1984). The common increase in tone of flexor muscles in the upper limb has also been attributed to disruption of corticoreticular projections. A powerful inhibitory influence is normally exerted from the cortex, over the pontine reticular nuclei, if this is lost there is excessive facilitation of alpha and gamma motoneurons of the upper limb flexor muscles and lower limb extensors (Brown, 1994).

The vestibulospinal tracts originate in the vestibular nuclei and carry information for the reflex control of balance and posture from the vestibular labyrinth. There is little evidence for significant projections from the cortex to these nuclei (Kuypers, 1981). Most stroke patients have cerebral infarcts and consequently do not suffer direct disruption to this system.

The tectospinal tract originates in the superior colliculus of the mid brain. It is the only medial brain stem pathway to project contralaterally and descends only a short way in the spinal cord (Kuypers, 1981). Its function is to coordinate head and eye movements. Such orienting is essential for initiating reaching but the tract probably has no direct influence over the motoneurone pools supplying the arm muscles.

The medial pathways may be thought of as working in parallel to the anterior CST. Their influence over the proximal musculature may explain why in many stroke patients there is sparing of gross arm function. However there are a significant number of cases who suffer complete paresis of the limb, and a lesser number who exhibit weakness at the shoulder but not at the hand. These difficulties are presumably caused by disruption to projections from the cortex and brainstem.

Kuypers' lateral pathways were the CST and the rubrospinal tract. The latter

originates from the red nucleus, decussates in the midbrain and closely intermingled with the fibres of the lateral CST, it descends in the dorsolateral funiculus of the spinal cord. It terminates in the lateral portion of the intermediate zone and among the motoneurone pools of distal muscles. Some of the fibres connect directly with motoneurons. In cats and monkeys it has been found to be important in controlling reach and grasp movements (Alstermark, Lundberg, NorrSELL and Sybirska, 1981; Lawrence and Kuypers, 1968b). Recordings from cells within a region of the magnocellular red nucleus in monkeys that were trained to perform a variety of upper limb and finger pressing tasks, have revealed especially strong relationships with movements of the thumb and fingers. Similar to findings of CM cell behaviour, discharges red nucleus cells were found to be highly correlated with movement onset, velocity and duration of movements (Gibson, Houk and Kohlerman, 1985a,b; Cheney, Mewes and Fetz, 1988). However in contrast to CM cells the red nucleus cells may be more closely associated with postural control of the hand and with movements of digits acting as a group, rather than with more precise independent finger movement (Houk, Gibson, Harvey, Kennedy and van Kan, 1988). In man the rubrospinal tract is very small (Nathan and Smith, 1982). It is thought that its function has largely been assumed by greater development of the CST.

The evidence from the anatomy depicts a rather unforgiving picture. In man the lateral CS system provides the only means of voluntary activation for distal muscles. It may also be the only supraspinal input that is focused enough to bring about fractionated movement control. There appear to be parallel influences acting to control proximal muscles: from the medial pathways and from both anterior and also possibly from lateral CST. The relative contributions each pathway brings to control the different motoneurone pools is still largely unknown. It is probably the balance of activity in these different pathways that determines the level of spared function after stroke.

1.6 Mechanisms for recovery.

The neurones that are interrupted by stroke degenerate in both antero- and retrograde directions from the lesion (Danek, Bauer and Fries, 1990). Axon regeneration does not appear to be a mechanism for recovery that is available to the mature central nervous system (David and Aguayo, 1981; Schwab and Thoenen, 1985; Carbonetto, Evans and Cochard, 1987; Schnell and Schwab, 1990), yet in many cases motor recovery takes place to some degree after stroke. In a small proportion of patients quite remarkable gains are achieved. How does recovery happen? How did the college professor who despite extensive loss of CS fibres, eventually learn to type with the affected hand (see Introduction, 1.1, Bach y Rita, 1980). Was this task, which required good independent finger movement, accomplished through the influence of the few remaining myelinated CS fibres; estimated by post-mortem measurements as only 3%? It seems unlikely. An alternative, classical idea is that surviving brain circuits might somehow "reorganise" to take over the functions of the lost system (Luria, 1963). For example, perhaps increased input from the medial pathways, could compensate for the loss of CS connections to motoneurones. Answers to these questions have come piecemeal from animal lesion studies, clinical cases and more recently from Positron Emission Tomography (PET) studies and investigations using TMS. The latter will be dealt with in detail towards the end of this chapter; this section will concentrate on evidence for reorganisation of the descending motor pathways from the three former sources. As an aid to understanding how reorganisation might be achieved the neuronal mechanisms that might allow adaptation will also be outlined.

1.6.1 Animal Lesion studies

Lawrence and Kuypers (1968a) lesioned the CSTs bilaterally at the level of the medullary pyramid in rhesus monkeys. In eight animals the lesions were considered complete and were achieved with minimal disruption of other fibre systems or brainstem

structures. At first, the monkeys were unable to pick up food, *"they reached with their arms towards food but their hands remained limply extended"*. After about six weeks however they were able to reach and grasp, but their ability to move digits individually to provide precision was permanently lost. In five other monkeys the lesions were incomplete and these animals showed a similar recovery pattern but they regained greater agility and more discrete movements. However, they did not achieve normal dexterity. Other monkey lesion studies in which the CSTs were cut at the pyramids (Hepp-Reymond, Trouche and Weisendanger, 1974; Chapman and Wiesendanger, 1982), or at the cerebral peduncle (Bucy, Ladpli and Ehrlich, 1966) have yielded accounts of initial paralysis followed by recovery of hand function over a few weeks. The level of skill regained has varied but these authors report recovery of precision grip, albeit with some clumsiness and reduction in speed. In many cases, after the experiment, the extent of the lesions were examined histologically and found to be incomplete. It is difficult to compare across studies but these authors all observed that the degree of recovered hand function corresponded with the extent of the lesion. Those with more spared fibres making a speedier and more complete return of function. 15% of fibres remaining was sufficient to allow precision grip and normal speed of movement to be regained (Chapman and Wiesendanger, 1982). In the macaque monkey, it therefore seems that if the CST is completely destroyed then the ability to move fingers individually to grip with precision is completely lost, but if just a small proportion of fibres are left intact this fine control may be recovered.

In contrast to the Lawrence and Kuypers (1968a) experiment, the lesions in the other studies have mostly been made unilaterally or in two stages if bilateral. Also in some investigations the animal's performance was put to the test frequently over the course of the following weeks, so they were encouraged to achieve precision tasks. In addition to environmental or training differences, one possible explanation for the

bilaterally lesioned animals' poorer recovery is that any ipsilateral CS projections to distal musculature would also have been lost. Although evidence for such a projection to ipsilateral motoneurons of distal muscles is so far missing, this possibility cannot be ruled out. There may be some connections made via interneurons (Goldring and Ratcheson, 1972; Lemon, Hanby and Porter, 1976; Matsunami and Humada 1981; Tanji, Okano and Sato, 1988).

The animals with unilateral lesions made at the level of the medullary pyramids made remarkably fast recoveries. Severe paresis lasted only a few days and they had reached a good level of function within six weeks of injury. It is possible that the initial more severe and widespread weakness was due to temporary disruption of intact descending fibres caused by oedema following the surgery. The dispersal of the oedema would explain the very rapid recovery of the first few days.

Evidence for reorganisation of function between different descending fibre systems has come from serial lesion experiments. Lawrence and Kuypers (1968b) performed further lesions on monkeys that had recovered from bilateral CS lesions (1968a). Four animals had sections made to the medial brainstem pathways. These operations primarily affected proximal muscle strength and postural control. Despite their disabilities, within twenty four hours the animals could hold pieces of food and soon recovered manipulatory abilities to a level that was comparable with that following their recovery from the CS lesions. This suggests that the recovery of hand function after interruption of the CS pathways could not have been mediated by the medial brainstem pathways.

In a second group of four monkeys the rubrospinal tract was cut on one side at the level of the medulla oblongata. These animals suffered weakness of the upper limb ipsilateral to the lesion. They lost the ability to use the limb independently of any body movement. Only when the other arm was restrained would the animal attempt to use it and then the movement was by pendular action rather than being well controlled at each

joint. Those with complete lesions did not recover. In contrast monkeys that had rubrospinal sections without prior CS damage quickly recovered hand function. It seems then, that recovery of function following the initial CS lesions may have been due to an increased contribution from the rubrospinal system. The converse might also hold true, recovery from a rubrospinal lesion may occur because of increased corticospinal influence. If both systems are lost recovery of hand function does not occur in monkeys.

Serial lesions in cats have shown even more substitution of function between pathways. When both CS and rubrospinal systems were sectioned, the reticulospinal tract eventually allowed cats to regain the ability to take food by grasping it with the toes and lifting it to the mouth (Alstermark et al., 1981, Alstermark, Lundberg, Pettersson, Tantisira and Walkowska, 1987). The experiments demonstrate that different pathways can assume the functions of damaged ones, but it appears that monkeys are more dependent on the CS and rubrospinal pathway than cats.

1.6.2 Clinical case studies

Seldom have we had the opportunity to examine recovery of function after stroke with the benefit of information that defines clearly the damage to the descending pathways. This situation is certain to change as techniques that are useful for tracing connections in the brain, such as Magnetic Resonance Imaging, become more widely available (Danek, Bauer and Fries, 1990). Until recently most examples of reorganised motor pathways in humans have come from reports that combine the history of an individual's recovery with evidence from careful post-mortem examination after death (e.g. Bach y Rita, 1980) or from examining recovery of function following neurosurgery (e.g. Bucy, Keplinger and Siqueira, 1964). In an interesting illustration of the former, Fisher (1992) described two patients who having shown substantial motor recovery, including hand movement, after a stroke affecting one hemisphere, lost their recovered functions

following a second infarct affecting the surviving hemisphere. In both cases histological examination revealed bilateral infarcts that interrupted the CS projections. The obvious explanation was that after the first stroke recovered function was subserved by the contralateral corticospinal system. A report in Japanese agrees somewhat with this thinking (Kameyama, Mannen and Takahashi, 1963). The clinical findings of hemiplegia were related to variations in the crossing of CS fibres at the decussation that were found at postmortem. *"They found that the manifestations of hemiplegia were less in those cases in which there was more ipsilateral innervation by corticospinal fibres"* (these finding are quoted from Nathan, Smith and Deacon, 1990).

The idea that the healthy CS system can contribute to motor recovery has attracted considerable interest. It is one that can be tested directly with TMS. If ipsilateral CS projections are able to influence the motoneurone pools of the affected muscles then short latency EMG responses to stimulation of the ipsilateral cortex should be detectable. Perhaps the clearest cut instances for investigating this is in tests of patients who have had hemispherectomy (Benecke, Meyer and Freund, 1991; Cohen, Zeffiro, Bookheimer, Wassermann et al., 1991; Pascual-Leone, Chugani, Cohen, Brasil-Neto et al., 1992). These patients have one cerebral hemisphere removed to alleviate intractable epilepsy. Some also have infantile hemiplegia. Any motor function that they recover in the affected limb can only be mediated by ipsilateral CS projections or via projections from the remaining cortex to the brainstem pathways. Recovered movement has been found to extend to distal muscles in patients who have infantile hemiplegia, but not in those patients where after normal maturation, a brain tumour in adulthood led to the operation. An investigation comparing such patients found short latency responses to TMS of the remaining hemisphere in the ipsilateral proximal and distal muscles of the infantile hemiplegia patients. These responses were generally largest in the more proximal muscles. No short latency responses were present in the ipsilateral muscles of patients who had normal

development (Benecke, Meyer and Freund, 1991). This suggests that the recovered function could have been mediated by ipsilateral CS connections in the former but not in the latter. Similar evidence for ipsilateral CS projections has been found in subjects with hemiplegic cerebral palsy (Carr, Harrison, Evans and Stephens, 1993), but not in adult stroke patients (Palmer, Ashby and Hajek, 1992). This picture corresponds to the findings of CST lesions in cats during development. New CS and cortico-subcortical projections were made in neonatal operated animals, but not in those operated after the first 8 weeks of life (Armand and Kably, 1992). Thus it appears that new projections may be made only when the CNS is not fully developed.

1.6.3 Positron Emission Tomography (PET) scan studies.

The idea that the intact cortex is at least partly responsible for recovered hand function in adults who have had a stroke has not been completely ruled out. Recent Positron Emission Tomography (PET) scan reports of recovered stroke patients have reopened the debate. Chollet, DiPiero, Wise, Brooks et al., (1991) scanned six well recovered patients. In the pooled results they found greater than normal increases in cerebral blood flow in the intact cortex, when the patients performed sequential opposition movements of the thumb to each finger with the affected hand. Increased blood flow in a particular area of the brain is thought to reflect a greater metabolic demand resulting from increased synaptic activity within that region; in this case the healthy ipsilateral cortex.

The analysis of Chollet et al., (1991) was restricted to looking at the stroke patients results as a group and comparing the blood flow to normal. However, PET techniques have improved and it has become possible to detect regional cerebral blood flow (rCBF) changes in single subjects. Weiller, Ramsey, Friston, and Frackowiak, (1993) were able to compare changes in blood flow of eight individual stroke patients with mean reference values obtained from ten healthy volunteers. The patients they scanned all had

ischaemic infarcts within discrete areas of the internal capsule. They had all recovered well from an initial dense paresis and at the time of study, were able to perform the sequential thumb to finger task. The scans showed that each patient had a different pattern of redistributed rCBF when they performed the task. The changes implicated both the damaged and the intact hemispheres. All eight patients showed increased blood flow in the premotor area of the *intact* cortex when performing the task with the recovered hand. In addition four of them had increased blood flow in the intact primary motor cortex. Each of these four exhibited mirror movements of the unaffected hand during intentional movements of the affected hand. This behaviour is characteristic of several congenital disorders, and in some cases is thought to be mediated by abnormally branched CS axons that project bilaterally to homologous motoneurone pools on either side of the spinal cord (Farmer, Ingram and Stephens, 1990; Carr et al. 1993). PET cannot identify whether the increases in rCBF are related to activity in CS neurones or in cells projecting to the brainstem motor nuclei. It is conceivable that the increased rCBF observed was simply due to the movement of the normal hand, alternatively it might represent activity that is not directly related to motor output (Lemon, 1993b). In the case of increased blood flow in areas of the intact cortex, it could be that a cross cuing mechanism is occurring, whereby information processed in one hemisphere is made available to the other. Alternatively it could reflect increased excitation in the intact hemisphere that is the result of a reduction of inhibitory influences from the damaged cortex (Ferbart, Priori, Rothwell, Day et al., 1992).

Weiller et al. (1993) also found increases in rCBF in parts of the *damaged* hemisphere. In five patients who had suffered little or no problem with their facial musculature after stroke, the area of increased blood flow on the damaged side extended into the region of the motor cortex that is normally considered to represent face movements. Other cerebral motor areas from which CS projections originate, such as the

supplementary motor cortex, the premotor cortex and cingulate cortex, also showed increases in blood flow in some patients. It is tempting to accept these results as evidence that there is reorganisation within the CS system, but it cannot stand alone as proof of changes that are responsible for recovered function (Lemon, 1993b). However these PET results do tally with the findings from a study that related motor recovery with disruption to the CS fibres that originated from different motor areas in the cortex. Using a motor assessment that comprises a series of motor tasks that are designed to examine the function of axial, proximal and distal limb musculature separately, Fries et al. (1993) measured the motor recovery of 23 patients who had subcortical strokes. Accurate estimates of the lesion site were made from CT scans that were projected onto stereotaxic planes. Patients with lesions of the anterior or posterior limb of the internal capsule, plus caudate/putamen, were initially severely impaired but made good recoveries which included the return of hand function. Because fibres from different motor areas (i.e. motor cortex, premotor and supplementary motor areas traverse different parts of the internal capsule (see section 1.3.), small capsular lesions can disrupt the output from a distinct motor area. Patients with lesions in the anterior limb of the internal capsule would have lost connections from the supplementary motor area; whereas patients with lesions confined to the posterior limb would have suffered more disruption of projections from the motor cortex. The clinically similar motor deficits and recoveries observed following disruption of these different fibre groups is rather at odds with the many experimental observations suggesting that the different cortical motor areas are involved in quite different functions (see Humphrey and Tanji, 1991). Nevertheless projections from those areas that are unaffected by the infarct may have the capability to take over the functions of fibres that are lost from another area.

1.6.4 Résumé of evidence for reorganisation of the descending pathways

The animal lesion studies suggest that sparing of CS fibres is necessary for

regaining independent finger movement and that ipsilateral CS projections may also help. Monkeys recovered better voluntary arm and hand movements, after CS lesion, if the rubrospinal tract was left intact. The number of the rubrospinal projections in humans is very small and stroke patients may not have the advantage of this parallel system.

The clinical studies indicated the feasibility of other pathways taking on the role of damaged cortical projections. There appears to be more chance of acquiring hand function if the damage occurs before the CNS is mature (the Kennard principle, 1942), although proximal arm movement may be regained after lesions in mature brains. This may be as a result of increased influence from the medial brainstem pathways and/or corticoreticular projections from the intact hemisphere.

Lastly the PET scan studies have reinforced the idea that the intact cortex contributes to motor recovery. They have also demonstrated that there are areas of increased synaptic activity over the damaged cortex when patients are using the recovered hand. Increased cortical excitability in these areas could be related to the mechanism by which spared CS neurones, perhaps originating in other motor areas, reestablish lost hand function or by which other cortical projections take on the functions of lost neurones.

1.6.5 Neuronal Mechanisms for Cortical Plasticity

Given that reorganisation can take place after damage to the brain, how does it happen? How could neighbouring neurones take over the connections of those that have been lost and assume new influences over the motoneurone pools? They might do this by the activation of existing latent connections that are "unmasked", or by growth or "sprouting" of new intracortical connections with cells that project to the "disconnected" motoneurone pools (Kaas 1991; Jacobs and Donoghue, 1991; Lund, Sun and Lamarre, 1994; Darian-Smith and Gilbert, 1994).

Over the last decade the type of reorganisation seen in PET studies showing extended areas of representation (Weiller et. al., 1993) has been explored in many animal

studies (e.g. Jenkins and Merzenich, 1987; Pons, Garraghty, Ommaya, Kaas et al., 1991; Zarzecki, Witte, Smits, Gordon et al., 1993). In these experiments cortical reorganisation was brought about in response to peripheral denervation. For example after removal or syndactyly of a digit in raccoon, the neurones within the area of sensory cortex that represented that digit changed their function and became more responsive to afferent inputs from adjacent digits (Zarzecki et al., 1993). Because most of the results obtained from these mapping studies suggest that changes in representation are limited to a zone that is no wider than the extent of the dendritic trees of cortical cells (up to 3.5 mm in macaques), and because the reorganisation happens quickly, over hours and days, most investigators have favoured the interpretation that these changes are the result of potentiating previously existing connections (Kaas, 1991; Asanuma, 1991). The potentiation could be due to a reduction in intracortical inhibition that occurs as a result of the damage (Wall, 1987; Jacobs and Donoghue, 1991), or by increased excitatory influences (Asanuma, 1991).

The comparatively slow changes seen after stroke may be brought about by long term strengthening of previously weak connections or they might arise following the creation of new connections. Only very recently has evidence for new connections been found in cortex. A significantly greater than normal density of terminal branches has been measured in cat cortex in the weeks and months following binocular retinal lesions (Darian-Smith and Gilbert, 1994). Along with the new branching that extended over 2-3 mm, extra synaptic boutons were counted. Reorganisation by sprouting of terminals still accounts only for small extensions of area. In monkey primary motor cortex repeated and well distributed representations of cells projecting to influence the same muscle have been found to extend a cortical area over $\sim 6 \text{ mm}^2$ (Lemon, 1990). If terminal sprouting operates in adult human brains then 2-3 mm of growth might be sufficient to tap into other CS cells that facilitate the same muscle as the fibres lost by stroke and thus facilitate recovery

after small infarcts.

It is evident that the cerebral cortex can be remodelled by sprouting or unmasking that extends over a few millimetres. This plasticity may or may not be helpful for recovery of function. However the ideal way to ensure restitution of normal function would be by regeneration of the damaged axons. There is little axonal growth after central nervous system injury in adult mammals. Regeneration of neurones is prevented by inhibitory factors, possibly originating in neighbouring glial cells (see Bähr and Bohoeffer, 1994). Nevertheless given a permissive environment (in vitro) containing growth factors from the peripheral nervous system and/or anti-inhibitors, it has been shown that rat CNS axons can regenerate across lesion sites (David and Aguayo, 1981; Schnell and Schwab, 1990). Recently regeneration and functional recovery has been demonstrated in vivo. Spinal cord lesions made in adult rats, followed by treatment with antibodies to neurite growth inhibitors resulted in regeneration of both brainstem and CS axons. The good functional motor recovery in the rats was shown to be dependent on the axon regeneration (Bregman, Kunkel-Bagden, Schnell, Dai et al., 1995).

Many researchers have focused on the identification of molecules that influence cell survival, axon growth and guidance, during development (see Aubert, Ridet and Gage, 1995). Presumably the presence of such substances in the immature CNS explain the generation of anomalous but functional, ipsilateral CS projections that have been identified in experimental animals after neonatal lesions (Reinoso and Castro, 1989; Rouiller, Liang, Moret and Weisendanger, 1991; Armand and Kabley, 1992). In future restitution of function of CS and corticofugal axons interrupted by stroke may be possible by the introduction of factors necessary for cell survival, growth and connectivity into the damaged structures.

1.7 Transcranial Magnetic Stimulation (TMS)

Over the last ten years TMS has become established as a non-invasive and painless way of investigating the CST and as such has the potential to shed light on reorganisation of descending motor control after stroke. TMS was introduced by Barker, Jalinous and Freeston (1985) as an alternative to transcranial electrical stimulation. Transcranial electrical stimulation signified a breakthrough in neurophysiology, since it gave scientists their first opportunity to investigate human CS functioning during behaviour, but contrary to the claims of Merton and Morton (1980), it is in fact extremely uncomfortable.

TMS is based on the principle of electromagnetic induction - i.e. producing a current in a conductive object by using a moving or time varying magnetic field (Jalinous, 1992). An insulated coil of wire is placed over the head (see schematic, figure 1.2). A very large current (peaking at ~5000 A) is passed very briefly (100 μ s) from a high voltage capacitor through the coil and produces a magnetic field of about 2 tesla at maximum. The depth of the field's penetration, its strength and accuracy as a stimulator, depend on the pulse rise time, peak energy transferred to the coil and spatial distribution of the coil (Jalinous, 1992). The fields produced with simple circular coils are strongest at the centre and fall off rapidly and exponentially with distance. An idea of the level of accuracy for positioning the coil was provided by Hess, Mills and Murray, (1987). They found that the breadth of the effective field from a 90 mm diameter circular coil was about 50 mm in diameter. The magnetic field induces a current in the conducting tissue of the brain, and probably excites very large numbers of cortical elements, both axons and cell bodies (Amasson, Quirk, and Stewart, 1990; Edgley, Eyre, Lemon and Miller, 1990). The cortical cells excited include the cells of origin of the CST which produce a repetitive discharge (Mills, 1991). This repetitive discharge is probably similar to that produced by strong electrical stimulation of the cortical surface in non-human primates (Kernell and Wu, 1967). In this case a series of waves were recorded from the pyramids after a single

electrical stimulus was applied. The first wave was followed by others at intervals of about 1.5 ms. The first wave (known as the D wave) is thought to be the result of direct activation of CS neurons, and the subsequent waves (I waves) to be due to re-excitation of the same neurons possibly by trans-synaptic means. The descending volley from TMS may bring the motoneurons to threshold to produce a muscle contraction which can be monitored by surface EMG electrodes (Hess, Mills and Murray, 1987).

Several different pieces of evidence have led to the conclusion that TMS excites the fast CM component of the CST. Measurements of the latencies of potentials recorded directly from the tract in monkeys (Edgley et al., 1990; 1992; Baker, Olivier and Lemon, 1994) and from limb muscles in humans (Day, Dressler, Maertens de Noordhout, Marsden et al., 1989; Baldissera and Cavallari, 1993) are consistent with conduction times of large diameter CS neurones in man. In keeping with the greater number of CM neurones terminating in the motoneurone pools of distal muscles (Porter and Lemon, 1993), responses are most easily obtained in the hand (Palmer and Ashby, 1992). Recordings from human single motor units have yielded increased firing probabilities at short latency after the stimulus, with two or three sub-peaks. The latencies of these sub-peaks in the post-stimulus time histogram, are 1.4-1.8 ms apart and are believed to represent the effects of a sequence of monosynaptic EPSPs at the motoneurone that are generated by the repetitive discharge of CS cells (Mills, 1988; Day et al. 1989; Boniface, Mills and Schubert, 1991).

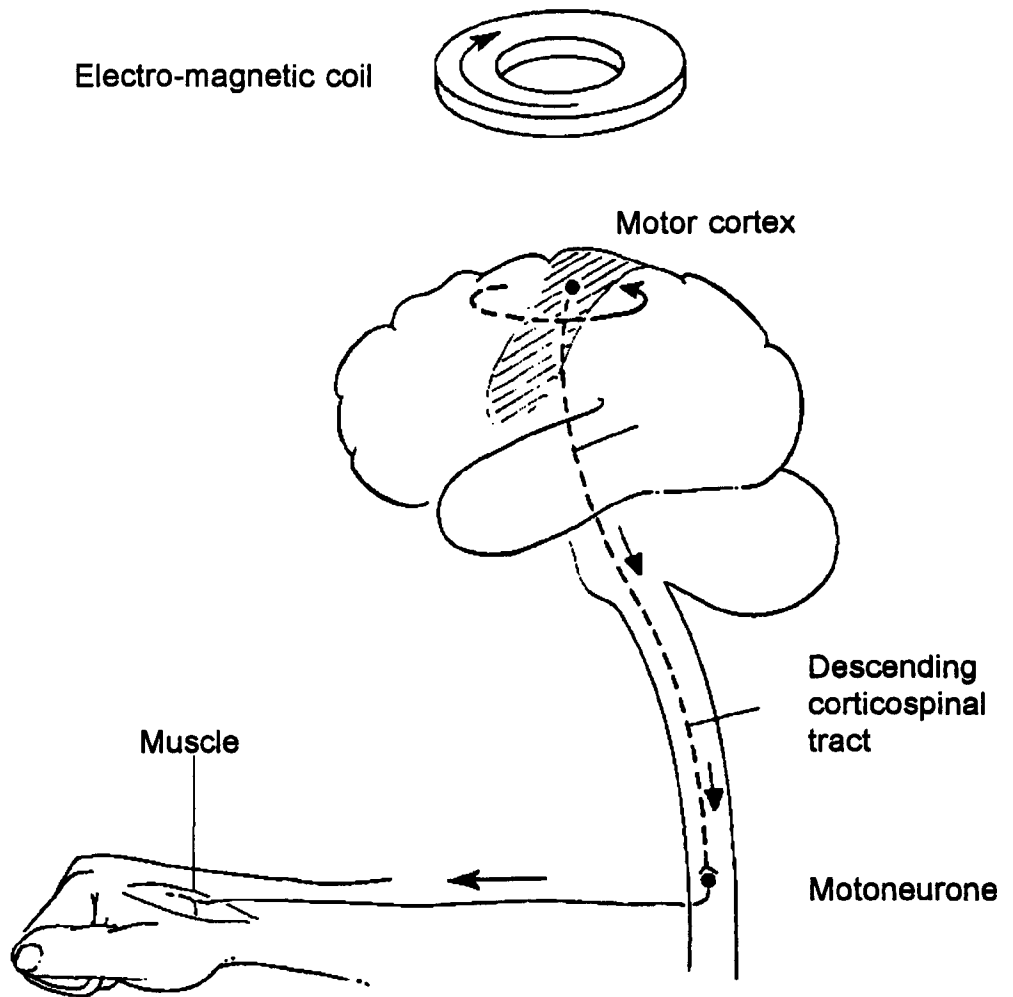


Figure 1.2 Schematic representation of the mechanism of action of TMS

The current in the coil generates a magnetic field which induces a secondary current in the conducting tissue of the brain. This excites cells of the motor cortex producing a repetitive discharge which descends to the spinal cord. This discharge may transynaptically activate the α -motoneurone thus producing a muscle contraction that can be monitored by surface EMG electrodes.

1.7.1 Safety

The prospect of applying large, albeit brief, currents close to the head inevitably gives rise to questions about the safety of TMS. Could it damage the brain? Since its introduction in 1985 many thousands of people have been tested using low repetition rate (< 1 Hz) magnetic stimulators without any side effects. So far studies that have addressed the question of safety in a systematic manner have found no detrimental effects on higher cognitive functions, or blood pressure and heart rate (Bridgers and Delaney, 1989, Eyre, Flecknell, Kenyon, Koh and Miller, 1990; see Chockroverty, Hening, Wright, Walczak, Goldberg et al., 1995).

A particular area of concern has been the risk that TMS might precipitate epilepsy. The basis for this fear has stemmed from the kindling of epileptic foci in experimental animals after repeated electric shocks (see Chockroverty et al., 1995). In fact kindling has not been induced in animals at frequencies of less than 10 Hz. A review of the literature revealed that the induction of seizures, following low repetition rate magnetic stimulation, is extremely rare, even in patients who have epilepsy (Chokroverty et al., 1995). Because epilepsy unfortunately sometimes develops after stroke, it is worth noting that in a large TMS study of 118 stroke patients with no previous history of epilepsy, two patients experienced a seizure (Heald, Bates, Cartlidge, French and Miller, 1993a). In both of these cases the incident occurred more than 4 weeks after TMS. Since the natural incidence of epilepsy after stroke is thought to be between 6% and 19% (Black, Norris and Hachinski, 1983; Berger, Lipton, Lesser, Lantos and Portenoy, 1988, Hauser, Ramirez-Lassepas, Rosenstein, 1984; Olsen, Hogenhaven and Thage, 1987; Shinton, Gill, Melnick, Gupta and Beevers, 1988), the seizures occurring in the two patients under study could well have been unrelated to TMS.

1.7.2 Differences between responses to TMS found in proximal and distal upper limb muscles.

Our understanding of the influence of CM projections in man has progressed substantially since TMS was introduced. It has been valuable in both corroborating and adding to the evidence indicating that there are important differences in the cortical control of different muscle groups. Palmer and Ashby (1992) were among the first to investigate differences in the facilitation by TMS of proximal and distal motoneurons. Using stimulus intensities that were just below the level required to obtain a twitch in the voluntarily contracted first dorsal interosseous (1DI), they tested the effects of TMS on single low threshold motor units that were firing steadily. The peristimulus time histograms (PSTHs) obtained from motor units in different upper limb muscles revealed stronger facilitation of distal muscles than proximal muscles. The largest responses were seen in 1DI. Responses of forearm muscle responses were slightly smaller. Biceps motor unit effects were only 37% as strong as 1DI. Triceps and deltoid motor units tended to be rather unresponsive to TMS and some were inhibited. These results were not simply explained by the position of the coil over the motor cortex. Palmer and Ashby used a large diameter coil that would have excited a large area of cortex. Moving the coil to various scalp positions over several centimetres had previously been found to have no effect on the order in which muscles were recruited by increasing the stimulus intensity (Brouwer and Ashby, 1990). The larger EPSPs which caused the greater responses in distal than in proximal motoneurons probably result both from there being larger numbers of CS neurones terminating amongst the hand muscle motor nuclei and because individual CM neurones projecting to distal motoneurons produce larger unitary EPSPs than do those projecting to proximal motoneurons (Porter and Lemon, 1993).

Inhibitory effects are evident in EMG recordings of distal muscles at lower TMS intensities than those that are required to produce motor evoked potentials (Ellaway,

Davey and Maskill, 1993; Davey, Romaiguère, Maskill and Ellaway, 1994). Although there appeared to be either an inhibitory effect, or no effect of TMS on deltoid motoneurons in Palmer and Ashby's (1992) investigation, they did use low stimulus intensities. Other investigators have obtained short latency excitatory responses in deltoid, with higher intensities (Colebatch, Rothwell, Day, Thompson and Marsden, 1990; Carr, Harrison and Stephens, 1994).

Voluntary contraction of a muscle greatly enhances its response to TMS (Hess, Mills and Murray, 1987; Baker, Olivier and Lemon, 1995). There is evidence that much of the difference in amplitude and latency observed between responses to TMS in resting and active muscles are due to facilitation at spinal level (Hess, Mills and Murray, 1986a; Day, Rothwell, Thompson, Dick et al., 1987; Maertens de Noordhout, Pepin, Gerard and Delwaide, 1992). However the "resting" or relaxed muscle state covers a wide range of excitability levels within the motoneurone pool: the membrane potential of a hyperpolarised motoneurone can be anywhere between -90 mV to just below its firing threshold at -50 mV. This was demonstrated in a TMS study of motor unit discharge, in which subjects who maintained silent EMG recordings from intrinsic hand muscles learned to raise the excitability of the motoneurons of a selected muscle (Gandevia and Rothwell, 1987). Once the motoneurone pool is active, it is possible that any further differences in facilitation seen with TMS may reflect the size of the CM population that is active during the task (Mazzocchio, Rothwell, Day and Thompson, 1994; Baker, Olivier and Lemon, 1995).

The relationship between response amplitude and level of contraction has been found to differ between muscles. Response amplitudes in intrinsic hand muscles rise rapidly with increasing muscle activity and reach a plateau at or before 20% of the maximum voluntary contraction (Hess, Mills and Murray, 1987). In contrast response amplitudes from biceps did not show this tendency to saturate at low contraction levels,

but instead exhibited a more gradual rise with increasing effort (Kischka, Fajfr, Fellenberg and Hess, 1993). These findings are in keeping with the functions of the different muscles groups and may reflect a variation in the influence of CS cells for different levels of muscle activity. Fine control of finger muscles is needed at low forces to carry out delicate and precise tasks (see Evarts et al., 1983). The control requirements of a muscle like biceps are disparate. It is used primarily to lift the forearm against gravity, often when it is loaded, and so its accuracy requirements are not so biased towards low forces.

1.7.3 Ipsilateral responses to TMS.

In addition to the short latency contralateral effects, late responses to TMS have been observed bilaterally in shoulder muscles: deltoid and pectoralis major (Colebatch, Rothwell, Day, Thompson and Marsden, 1990). Small late ipsilateral responses in proximal arm muscles have also been observed when TMS was specially focused onto one hemisphere (Wasserman, Fuhr, Cohen and Hallett, 1991). The increased latency may reflect the influence of more indirect pathways on proximal musculature, possibly via cortico-reticular projections. Alternatively the longer conduction time might reflect responses mediated by callosal fibres to the opposite cortex (Ferber et al., 1992; Meyer, Rörich, Gräfin von Einsiedel, Kruggel and Weindl, 1995).

Some researchers have looked for ipsilateral responses in hand muscles, without success (Wasserman et al. 1991, Carr, Harrison and Stephens, 1994). However Wasserman, Pascual-Leone and Hallett, (1994) have reported weak ipsilateral responses in 1DI of six subjects. The onset of ipsilateral responses were 4 ms later than the contralateral responses and were elicited from coil positions over the motor cortex that were different from the optimal position for obtaining a contralateral response in 1DI. The short latency difference rules out the possibility that responses were mediated through callosal fibres. Such a delay could be due to temporal summation at the motoneurons; if TMS is able to excite only a small number of ipsilaterally projecting CS cells then

repeated volleys would be needed to bring the motoneurons to discharge. Alternatively, responses to TMS in ipsilateral hand muscles may be mediated by slowly conducting CS fibres, or indirectly through interneurons.

1.7.4 Task related variation in the size of responses to TMS.

TMS has also provided a unique means to investigate CM function in man during the performance of different tasks. The amplitude of short latency EMG responses to TMS in an intrinsic hand muscle is altered according to the task in which it is involved (Datta, Harrison and Stephens, 1989; Flament, Goldsmith, Buckley and Lemon, 1993; Schieppati, Trompetto and Abbruzzese, 1996). TMS was delivered while fourteen young adult subjects performed an isometric abduction of the finger movement, a pincer grip, a power grip, a span grip (fingers spread to encircle a petri dish) and a rotatory grip exerted on a bottle top (Flament et al., 1993). Clear, consistent and statistically significant changes in response amplitudes were observed. Greater response amplitudes were recorded in 1DI during the more functional grip tasks than during isolated abduction of the index finger. In most of the fourteen subjects strikingly large responses were found for pincer and/or rotatory grip tasks. Flament et al. (1993) suggested that the variation in response amplitudes might be due to the facilitation by TMS of different sub-populations of CM cells during each task. It is known from direct recording of CST activity that the susceptibility of the CS system to direct excitation by TMS is related to the level of excitatory synaptic input (Baker, Olivier and Lemon, 1994, 1995). If more neurones within a particular zone of cortex are already active, there is a greater chance of their being discharged by TMS, which in turn leads to a larger CS volley and EMG responses. However EMG responses reflect the net facilitation and inhibition from both cortical and spinal levels and an alternative explanation of the variation in results across tasks would be that the modulation was due to changes in spinal reflex mechanisms. This was to some extent controlled by the maintenance of a constant level of motoneuronal excitability

across the tasks, which was achieved by keeping the level of baseline EMG activity in the 1DI steady at 5% of the maximum voluntary contraction (MVC). Since the earliest component of the response to TMS is thought to be mediated by the CM system, keeping the motoneuronal excitability level constant in this way should control for any changes in the excitability of spinal mechanisms.

Larger responses to TMS in 1DI and a thumb muscle, *opponens pollicis*, were found during pincer grip than during a power grasp (Schieppati et al., 1996). Responses in either 1DI or *opponens pollicis*, but not both, were increased in individual subjects. In addition to controlling for modulation at the spinal motoneurone level by including in their analysis only responses that were preceded by similar background levels of EMG, these authors tested H-reflexes in some subjects and found no difference in the size of reflex responses between the two tasks. Schieppati et al. (1996) were therefore confident that the modulation of responses to TMS was not a function of differential excitability within the motoneurone pools during the two tasks.

Datta, Harrison and Stephens, (1989) compared, in 12 young adults the responses to TMS in 1DI during abduction and power grip, both maintained at 20% MVC. In contrast to the results of Flament et al. (1993), they found responses in abduction were greater than in the power task. The results may have conflicted due to methodological differences between the two studies. The trial by trial variability of response amplitudes to TMS is notoriously high. Datta et al. (1989) recorded far fewer responses so any spuriously large or small stimuli would have had a greater effect. Differences in the level of the background contraction, stimulation strength and the method used for maintaining the position of the coil, may also have affected the results, (Hess, Mills and Murray, 1987).

TMS has also been used to probe modulation of CM input to motoneurons during different phases of the same task. Lemon, Johansson, and Westling (1995) looked at

response amplitude variation when subjects reached for an object weighing 0.5 kg, grasped it, between finger and thumb, lifted and held it steady in the air. The response amplitudes, normalised to control levels of EMG taken from trials with no stimuli, were greatest in 1DI at the time just after initial contact of the digits with the object, when the grip force begins to develop. They were smallest during the steady hold phase. It is possible that the large responses during the initial grasp phase reflected the sharp rise in the number of CM cells that would have been discharging to produce the necessary increase in rate of grip force (see section 1.4.4). Part of this recruitment probably results from the sudden increase in afferent feedback from the hand after contact with the object. There is a good correlation between sensory input and activity of CS cells in the motor cortex (Lemon and Porter, 1976; Asanuma, 1981). Although spinal circuits are also very responsive to afferent input, Lemon et al. (1995) suggested that it was more likely that the CS activity following contact with the object was reflected in the responses to TMS because there were clear dissociations between response amplitudes and the variation in background EMG. Any effects of afferent input to the level of motoneurone excitability would have been apparent in the control trials in which the task was completed without TMS. The modulation with task was also very sensitive to the intensity of TMS also suggesting a cortical origin.

In monkey experiments it is possible to obtain a direct answer to the question of whether cortical excitability influences the response to TMS. Baker, Olivier and Lemon (1994) developed a method of recording the CS volley directly from the medullary pyramid. Using this approach they looked at the amplitude of the CS volley evoked by TMS across different phases of a precision grip task (Baker, Olivier and Lemon, 1995). The size of the volley began to increase shortly before the thumb and finger force increased and plateaued to a maximum during the steady hold phase of the task.

Task dependency in man has also been found in the responses of proximal arm

muscles (Abbruzzese, Morena, Spadavecchia and Schieppati, 1994; Schieppati et al., 1996). The response amplitudes in anterior deltoid and biceps brachii were found to be larger in tasks that required careful matching of force than in tasks which had no accuracy constraints (Schieppati et al., 1996). The size of responses in elbow muscles were also found to be dependent on the type of muscle contraction being performed (Abbruzzese et al., 1994). Brachioradialis and biceps had larger responses when contracting isometrically than when performing eccentric (lengthening) contractions. Brachioradialis also had even larger responses when contracting concentrically (shortening). The tasks were arranged so that the antagonist triceps remained quiet and by using different weights the experimenters made sure that comparable levels of EMG activity were maintained in the flexors across tasks. As an indication of the influence from spinal control mechanisms, Abbruzzese et al. (1994) also obtained H reflexes from some of their subjects while they were performing the tasks. The reflex amplitude was modulated in a pattern that paralleled the variation in responses obtained from TMS. It appears that in the case of elbow flexors, changes in the excitability of CM neurones are of less consequence than those of the spinal circuitry. This result is not really surprising considering that the influence of the CM neurones is substantially smaller for proximal than for distal muscles (Palmer and Ashby, 1992).

1.8 The use of TMS to investigate stroke patients.

The potential of TMS for investigating stroke patients was quickly recognised. It has been employed to verify the effect of disruption to the CST on the motor function of stroke patients' and it has been investigated as a prognostic indicator for recovery after stroke. In addition some researchers have taken advantage of its potential to investigate mechanisms that might contribute to recovery. The TMS studies were preceded by early studies using Transcranial Electrical Stimulation (TES). TMS has proved to be a better

tool for eliciting responses in stroke patients than TES (Berardelli, Inghilleri, Cruccu, Mercuri and Manfredi, 1991). This may be because TES, as well as activating CS neurones within the cortex, spreads to excite the axons below the level of the motor cortex (Edgley et al. 1990, 1992; Burke, Hicks, Gandevia, Stephan et al., 1993). Responses to TES are not as sensitive to the level of contraction and type of task as are responses to TMS, probably because TMS acts only at the cortical level. However TES has been useful for making distinctions between patients and has been sensitive enough to detect change in responses over time. Studies using TES are included in this review.

1.8.1 Characteristics of stroke patients' responses to transcranial stimulation.

TMS and TES provided the first means to investigate how interruption to the fast connections between motor cortex and the spinal motoneurone pools contribute to the clinical picture of motor impairment in groups of stroke patients. The response characteristics measured have usually been their presence, amplitude and latency, or extrapolated central motor conduction times (CMCT). The latter is normally derived by subtracting the peripheral conduction time from the onset latency of the response to TMS (see Rothwell, Thompson, Day, Boyd and Marsden, 1991; Heald et al., 1993a). Subtraction of the peripheral component eliminates variation caused by limb length. The peripheral conduction time is usually measured from responses to magnetic stimulation with the coil held over the spine at low cervical level, but since these are thought to excite the proximal motor roots, the resulting CMCT includes a small peripheral component as well as synaptic delay of approximately 1 ms (Hess, Mills and Murray, 1986b; see Murray, 1992).

Early investigations classified patients according to severity, as assessed by fairly cursory clinical examinations, and compared responses to TES with those from normal subjects. Responses in the weak muscles of the most severely affected stroke patients were usually absent. In less affected patients, or in patients investigated sometime after

stroke, responses were delayed, of smaller amplitude and had higher thresholds than on the unaffected side. Responses from the unaffected side were normal (Beredelli, Inghilleri, Manfredi, Zamponi and Cecconi, 1987; Thompson, Day, Rothwell, Dick et al., 1987; Uozumi, Tsuji and Murai, 1991). Having established that there was variation in the responses of stroke patients more recent studies have correlated weakness with responses to TMS in patients with heterogeneous lesion sites (Homberg, Stephan and Netz, 1991; Escudero, Sancho, Escudero, Lopez-Trigo and Lominchar, 1992; Heald, Bates, Cartlidge, French and Miller, 1993a,b). Despite using a number of sensitive assessments of strength and hand function, most of these studies have not refined the original correlation between clinical impairment and response characteristics. Their reports follow the pattern observed by the early TES studies (Beredelli et al., 1987; Thompson et al., 1987): with individuals lacking responses exhibiting severe motor impairment, those with small and late responses and high thresholds, having severe or moderate impairment and patients with normal latency having relatively mild clinical signs. Escudero et al. (1992) were more explicit in their determination of the level of strength that was representative of each class of response. They found that in 20/26 cases of patients who were unable to activate abductor pollicis brevis (i.e. grade 0 or 1, MRC scale) responses were not present. Responses were recorded in practically all cases in which there was contraction of the muscle (35/36 patients with grade 2 or more). Patients with normal or near normal strength (grade 4 or 5) had normal response latencies and thresholds. Only the amplitudes of their responses were significantly smaller than normal.

1.8.2 Responses and lesion site.

Occasionally some exceptions to the pattern described above have been observed: some patients with very poor motor function had normal CMCT (MacDonell, Donnan and Bladin, 1989; Dominkus, Grisold and Jelinek, 1990; Chu and Wu, 1992). It may be that the inclusion of stroke patients with a large variation of lesion sites in many studies has diminished the correlation between various parameters of responses to TMS and motor performance. Investigations of the effects of lesion site on responses to TMS or TES have shown that prolonged CMCT is more prevalent in those patients who have capsular lesions than those with cortical infarcts. Patients with cortical lesions are likely to have either no responses, or responses of normal latency (MacDonell et al., 1989, Abbruzzese, Morena, Dall'Agata, Abbruzzese and Favale, 1991; Chu and Wu, 1992). Many severely affected stroke patients have large infarcts involving subcortical as well as cortical areas. In these patients responses are usually absent (Escudero et al., 1992). However if the lesion is small the presence of responses to stimulation probably depends on the cortical area involved. It has been suggested that the occurrence of poor hand function in patients who have normal responses may result from cortical lesions that do not extend to subcortical areas (MacDonell and Donnan, 1992). Presumably in these cases the damage may have effected commands upstream of the CS neurones, e.g. in areas that have an important role in planning movement or integrating sensory information.

The idea that cortical damage can cloud the relationship between CS involvement and impaired motor function is supported by the results of a study which investigated only patients with pontine infarcts. Particularly good correlations were found between CMCTs, response amplitudes and subjective estimates of hand strength in these patients (Ferber, Vielhaber, Meincke and Buchner, 1992).

1.8.3 Responses to TMS during recovery and as a predictor of recovery.

Responses to TMS reappear when patients regain voluntary contraction of a given muscle (Dominkus, Grisold and Jelinek, 1990; Chu and Wu, 1992; Escudero et al. 1992; Heald et al., 1993a,b). The largest longitudinal study of recovery using TMS was carried out by Heald et al. (1993b). They tested 118 patients at regular intervals for 12 months after stroke and looked for changes in the CMCT derived from EMG responses in arm and hand muscles. Some, but not all patients who lacked responses at the first test, (within 3 days of stroke), were found to have responses at later tests. Some with prolonged conduction times early on, improved to achieve normal delays. Many patients in all groups recovered some motor function, but those who had no responses to begin with did not recover so completely as those who had responses of prolonged or normal latencies at the first test. The changes in the presence of responses and in CMCT of responses were observed in both the distal and proximal muscles investigated and no distinctions were made between them, except that the initial responses in the thenar muscles demonstrated the highest correlation with clinical and functional measures of recovery at the one year assessment.

Heald et al. (1993b) were particularly interested in determining the value of TMS for identifying patients with a high probability of survival and functional recovery. Their results did reveal some value of the presence of responses tested within 72 hours of stroke for predicting motor recovery, level of independence and survival. For example 54% of patients with normal or delayed responses at the first test recovered normal hand function and 87% regained independence in personal care. The results of Heald et al. (1993b) confirmed and extended the findings of others who had hailed TMS or TES as being a useful indicator for recovery on the basis of their findings from smaller and shorter investigations (Macdonell, Donnan and Bladin, 1989; Dominkus, Grisold and Jelinek, 1990; Chu and Wu, 1992; Lissens and McKay, 1992; but see Murray, 1992). However

a large minority (15%) of patients who have no responses in the first week after stroke, have been observed to make remarkable recoveries (Escudero et al., 1992). With growing pressure on beds, hospitals are anxious to discharge patients as soon as possible (Cambridge and Huntingdon Health Commission, 1995). In making difficult decisions about which patients are likely to become independent enough to return home and which are likely to need long term care, it is important to have the best available prognostic indicators. TMS has not yet been tested against the clinical tools that are currently in use, and may not ultimately prove to be any better.

1.8.4 The use of TMS for exploring mechanisms for recovery.

To what extent is the reappearance of voluntary activity due to the recovery of CS influence? The obvious assumption is that the changed responses must signify some reorganisation within the CS system, but this is not the only explanation. The responses may have materialised as a result of change within some other system. In normal subjects responses to TMS are facilitated by background muscle contraction (Hess, Mills and Murray, 1987, Kischka et al., 1993; Mazzochio, Rothwell, Day and Thompson, 1994). In the relaxed subject TMS may fail to generate an EMG response because the descending CS volleys it elicits are too weak to cause discharge of the motoneurones supplying the muscle under investigation. Certainly the absence of an EMG response in a paralysed muscle cannot be taken as evidence that TMS is failing to excite a CS volley (Heald et al., 1993a). Thus the return of voluntary activation could reflect the recovery of other, non-corticospinal excitatory inputs to the motoneurone pool; the raised excitability at spinal levels provided by these inputs might well be sufficient to allow CS volleys excited by TMS to produce EMG responses. Given the very different influences of the CS system upon different upper limb muscles, this factor may vary considerably for different muscles, and can provide some useful clues as to the importance of the CS system for their voluntary activation.

Most TMS investigations of stroke patients have recorded EMG from hand muscles. The reports of those that have recorded from both proximal and distal muscles have tended to concentrate on a single muscle. Dominkus, Grisold and Jelinek, (1990) studied responses to TES in biceps and abductor pollicis brevis at three days and two months after stroke and assessed motor recovery with an index of upper limb strength. Changes were seen in the response characteristics in the two muscles, but unfortunately no indication of relative contribution of each muscle to the overall improvement in arm strength score was given. Heald et al. (1993a,b) recorded EMG responses from pectoralis major, biceps, triceps and thenar muscles. They found that the CMCT derived from the thenar muscles consistently demonstrated the highest correlations with strength and motor function measures, so they based their analysis predominantly on responses in thenar muscles. Perhaps the lesser correlations of the more proximal muscle responses provide a clue that the CS system is less important for their voluntary activation. The question remains: *How important is CS input for the recovery of different muscle groups?*

Some researchers have set out to test the hypothesis that the intact hemisphere may influence motoneurone pools of the affected limb and thus contribute to recovery (refer back to 1.6.2.) (Fries, Danek and Witt, 1991; Palmer, Ashby and Hajek, 1992). This is a good subject for investigation by TMS. The presence of ipsilateral responses to TMS in the affected limb would confirm that the motoneurons were receiving some input from the spared cortex. Palmer et al. (1992) looked at 10 patients who had recovered some elbow movement and whose strokes occurred between 7 and 57 months before the investigation. They found no short latency facilitation of ipsilateral motor units in biceps from stimulation of the intact cortex, although three patients had long latency facilitation. Palmer et al. (1992) concluded that fast ipsilateral CS pathways do not account for recovery in stroke. Other authors have observed individual cases with long latency ipsilateral responses from the intact cortex, but no short latency ones (Benecke, Meyer and

Freund, 1991; Homberg, Stephan and Netz, 1991; Thompson et al., 1987). Cortico-reticulospinal fibres were suggested as a possible route for mediating the long latency ipsilateral responses (Palmer, Ashby and Hajek, 1992; Benecke, Meyer and Freund, 1991).

A rather surprising result came out of a study by Fries, Danek and Witt (1991). In a well recovered patient they found short latency responses in the unaffected hand when the damaged hemisphere was stimulated at high intensity. Fries's group obtained similar results from other patients using TES. Again cortico-reticulospinal fibres were suggested as a possible route of mediation.

The results from these investigations have yielded a rather inconclusive picture. It seems that ipsilateral responses are uncommon, but it is not clear in cases where they are present whether they do represent a mechanism that is beneficial for recovery.

1.9 Objectives of this study.

An area that has been neglected is the impact of stroke on the modulation of responses to TMS across tasks. Since the responses evoked by TMS are sensitive enough to pick up differences in CM output according to task in normal subjects, it is interesting to see whether patients with a substantial loss of CM cells show task dependent responses. The present investigation started by looking at the task dependence of responses in patients who had already recovered some hand function after stroke and of a group of normal subjects who were closer in age to the patients than the young subjects who participated in the study of Flament et al. (1993).

The next and major part of my work was a longitudinal study of recovery. I wanted to understand better the mechanisms that contribute to recovery of hand and arm function. Because of the different effects of stroke on different muscle groups, it was important to compare responses from intrinsic and extrinsic hand muscles, as well as for muscles acting at the elbow and shoulder and to look for correlations between these

observations and the recovery of hand function assessed with a battery of tests.

Thirdly, special attention was paid to the existence of responses excited by TMS in *ipsilateral* muscles, because of the possible contribution of the undamaged hemisphere to recovery of function. In these longitudinal investigations, it was considered important to study a small, carefully selected cohort of patients with clear hemiplegic signs when first admitted and to follow these patients up at regular intervals over the first 12 months after stroke.

Somewhat surprisingly ipsilateral responses were elicited from both affected and unaffected hemispheres and proximal and distal muscles of some stroke patients. To establish whether this was due to pathology a thorough and systematic investigation of ipsilateral responses to TMS in normal subjects was carried out.

Contrasting results between the presence of responses to TMS in proximal and distal muscles and their functional recovery led to further investigations. Two paradigms were used to clarify the contribution of CS input to production of force in proximal and distal muscles in normal subjects: In the first the effect of increasing voluntary muscle activity on the amplitude of responses to TMS in 1DI, biceps and deltoid was investigated. In the second the increases in stimulus intensity required to recruit motor units in 1DI and deltoid were determined. The results of these two studies provided a means of examining the relationship between response amplitude and voluntary activity in the affected and unaffected shoulder muscles of three stroke patients.

The results of these different investigations highlight important differences in the cortical control of arm and hand muscles, and the effects of stroke upon this control. They further shed some light on the reorganisation of motor pathways after stroke, and suggest which aspects of this reorganisation may contribute to recovery of function.

CHAPTER TWO.

METHODS.

Methods that were common throughout the work are described here. Methodological details, protocols and statistical analysis that are particular to individual studies will be included in the relevant chapters.

2.1 Normal subjects and patients.

Normal subjects, aged 19 - 63 were investigated. None of them had epilepsy or a history of other neurological disorders. The patients, aged 21-77 had all been admitted to Addenbrooke's Hospital, Cambridge, with acute onset of neurological deficit of presumed vascular origin. None had suffered previous strokes. They were recruited following a first stroke and had impaired upper limb movement that was restricted to one side. All subjects and patients gave informed consent to the procedures used, which were ratified by the local ethical Committee.

2.2 Clinical assessments.

A number of tests were used to assess the patients' upper limb motor function. Hand function was determined by standardised timed tests, the ten hole peg test and a unilateral/bilateral hand function test and by grip strength (Turton and Fraser, 1986). The peg test gives an objective measure of gripping and transport operations and encompasses many different components of hand function, including speed, accuracy and coordination. The unilateral/bilateral test involves both unscrewing and screwing together nuts and bolts and requires a degree of intrinsic hand function. It is a rather lengthy test, so only the parts of the test that measured the time taken to unscrew nuts from a row of five fixed bolts were included. Power and pinch strength were measured using a Jaymar

dynamometer (Gilbertson and Barber-Lomax, 1994). The scores for all three tests were compared with normative data, and also with results from the unaffected side.

The longitudinal study involved some patients who were unable to perform the hand function tests. Since arm function was also of interest, the motricity index was used to provide an overall arm score (Demeurisse, Demol and Robaye, 1980; Wade, 1992, p154-155). The motricity scores are derived from new weights given to MRC muscle tests for shoulder abduction and elbow flexion, as well as a prehension test. In addition MRC muscle tests (Wade, 1992, p53-54) were performed for each of the muscles investigated. The Southern Motor Groups's Assessment (Ashburn, 1982), administered in a sitting position provided a means of assessing the patient's ability to adopt a series of limb postures that break out of the flexor synergy that is associated with some stages of recovery after stroke (Twitchell, 1951; Brunnstrom, 1970).

Proprioception was tested by asking the patient to copy with the unaffected limb a series of positions in which the tester placed the affected limb. This was done with eyes closed. Cutaneous sensation was tested by asking the patient to determine whether they could feel light touch over the hand and forearm, again without vision. In addition any perceptual problems or apraxia that was observed during the patient's Occupational Therapy were noted.

2.3 Surface EMG recordings.

Surface electromyograms (EMGs) were recorded using 10 mm ARBO electrodes placed with their centres 20-30 mm apart over the muscle bellies (electrode impedance $< 5\Omega$ at 1 KHz). All EMG signals were amplified (x500), but in investigations involving very low levels of EMG activity the gain was increased (x1K-x5K). The EMG signals were filtered (bandwidth 30 Hz - 5 KHz), and full wave rectified. The EMGs were captured via a 1401 interface (Cambridge Electronic Design) using SIGAVG software.

Data was digitised at 4 KHz. Sweeps were recorded for at least 70ms after the stimulus artifact. Sweeps of background EMG data (no stimulation) were interleaved with sweeps in which stimuli were delivered.

2.4 EMG feedback.

Feedback of EMG level during task performance was provided after rectification and R.M.S. smoothing of the EMG signal, and was displayed as a column of ten lights. The height of the illuminated column increased linearly with the EMG amplitude. Subjects were required to contract maximally, so that the feedback device could be set up to represent the required proportions of the maximum voluntary contraction (MVC). MVCs of each muscle were collected for 10 sweeps at the beginning of the experiment and then again at the end to check for consistency.

2.5 Tasks

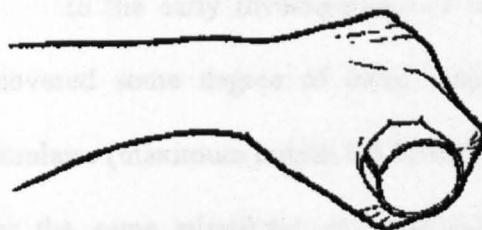
Four isometric tasks were selected for investigation: One "simple" task: index finger abduction and three "complex" tasks: pincer grip, power grip and a rotation grip (Fig. 2.1). The subject was seated with forearms resting on a table, the wrist pronated and the hand flat on the table. Index finger abduction was the control task; isolated contraction of the 1DI muscle abducts the index finger. In this task no other muscles were required to act. To restrict the movement to abduction of the index finger, the digits were separated with cushioned pegs between the thumb and index finger and between index finger and middle finger. The subject abducted the index and pressed against the peg. The other 'complex' tasks were functional grips requiring cooperation of the thumb and the other fingers; for these tasks the 1DI acted in synergy with other muscles. To perform the pincer grip, a staple remover was squeezed between the pads of the index finger and thumb.



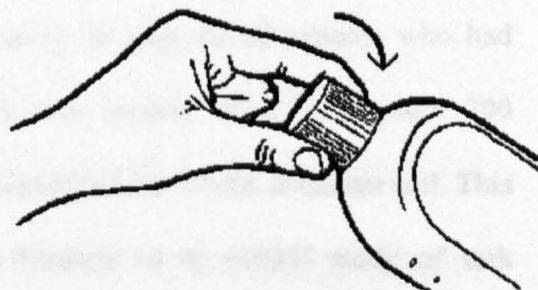
Abduction



Pincer



Power



Rotation

Figure 2.1 Diagrams of the tasks performed

Abduction was performed by using the index in isolation; all other tasks involved coordinated activation of two or more digits.

For rotation, the subject was asked to exert an isometric turning force on a bottle top (diameter 3 cm) held between the radial side of the index finger and the pad of the thumb and to exert the force towards the midline (i.e. clockwise for the left hand, anticlockwise for the right hand). For both pincer and rotation tasks, the ulnar fingers were curled into the palm. Power grip was performed with all the fingers flexed around a cylinder (diameter 4.5 cm).

2.6 Transcranial magnetic stimulation.

During the course of the work, more powerful magnetic stimulators and more focal coils became available. For this reason different stimulators and coils were used for the different studies (summarised in table 2.1).

In the early investigations of task dependency in a group of patients who had recovered some degree of hand function, TMS was applied using a Magstim 200 stimulator (maximum output 1.5 Tesla) with a standard circular 90 mm diameter coil. This was the same stimulator and coil used in the Flament et al. (1993) study of task dependence in normal subjects. Extensive investigations have demonstrated that the most effective coil position for eliciting EMG responses in hand muscles when using a circular coil is with its centre placed 2 cm behind and lateral to the vertex (Meyer, Britton, Kloten, Steinmetz and Benecke, 1991). The human motor cortex appears to be more sensitive when the induced current is flowing from posterior to anterior (Barker, Jalinous and Freeston, 1985; Jalinous, 1992). Therefore to obtain the best effects the coil was placed over the vertex, with its "A" side up for the right hand and "B" side up for the left, and then its position was slightly adjusted to the location at which the lowest threshold responses could be obtained in the gently contracting contralateral 1DI. The coil position was then marked on a tightly fitting rubber cap worn on the subject's head. Because even small displacements of the coil relative to the brain can result in large differences in

response amplitude (Hess, Mills and Murray, 1987), coil position had to be kept constant throughout the experiment. For the very first patient tested this was achieved with head fixation using a bite-bar system as described in Flament et al. (1993). Subsequent patients had the coil attached firmly to the head with velcro straps. The weight of the coil and its heavy cable were counterbalanced by elastic bands suspended from an overhead gantry. This arrangement allowed the patient some freedom of movement without disturbing the relative position of the coil on the head.

In later task dependency investigations: i.e. of a group of normal subjects, who were matched for age with the stroke patients investigated, the Magstim 200 magnetic stimulator fitted with a double cone (DC) coil was used. DC coils consist of two windings placed side by side producing a maximum induced electric field under the point where the two windings meet (Jalinous, 1992). Each winding of the DC coil had an inner diameter of 90 mm and outer diameter of 110 mm; the angle between the windings was 100°. The optimal coil position for obtaining responses short latency EMG responses in 1DI using DC coils is normally found with the junction region placed about 6 cm lateral to the vertex. The precise position was judged by both threshold and amplitude of the evoked response obtained in the gently contracting 1DI. This position was then marked either directly onto the scalp or onto a tight fitting wide rubber strip (Theraband) worn on the head and fixed under the patient's chin. The coil was then strapped to the head in the same way as was described above for the round coil. It was considered possible that the DC coil may not be suitable for detecting task dependency in responses. If, as suggested by Flament et al. (1993), the difference in response amplitudes during task performance reflects the level of activity in cells lying closer to the coil then changing to a coil with a different shape and focus may influence the results. To test this two young subjects were investigated using the DC coil (see below, section 2.8). Responses elicited by the of the DC coil were found to be just as task dependent as those evoked by the round coil.

The first fourteen patients in the longitudinal study were tested using a Digitimer D190 stimulator with a standard double cone coil, and maximum output of 1.5 Tesla (see table 2.1). Each coil had an inner diameter of 105 mm and an outer diameter of 142 mm, the angle at the junction region was 100°. During the course of the study a Magstim 200 stimulator with a double cone coil (outer diameter 110 mm, angle 100°) became available. This stimulator had the advantage of being more powerful (max. output 2.0 Tesla) and was found to be more comfortable than the digitimer. For these reasons the last eight patients recruited to the longitudinal study had TMS applied with the Magstim stimulator. All patients in the longitudinal study were retested only with the stimulator that was used for their first test.

The subjects and patients who participated in subsequent investigations of the presence of ipsilateral responses and in the experiments to determine the differences in cortical control between shoulder and hand muscles, had TMS applied with the Magstim 200 stimulator and DC coil. To test for ipsilateral responses in some subjects and patients the responses to stimulation with a hand held small butterfly (SB) coil were investigated. With an inner diameter of 35 mm and outer diameter 75 mm for each winding, this coil is designed for hemispheric-selective stimulation.

Throughout all of the investigations stimuli were delivered at a safe rate of one every 3-5 seconds.

Table 2.1 Stimulators and coils used in studies.

Study (chapter no.)	Stimulator	Coil
Chapter 3. Task dependency recovered stroke patients Ipsilateral responses in 1DI, same patients	Magstim 200 maximum output 1.5 Tesla	Circular 90 mm outside diameter Small butterfly (SB) outside diameter of each winding 75 mm.
Chapter 3. Task dependency in normal subjects and in recovering patients selected from longitudinal study.	Magstim 200 maximum output 1.5 Tesla	Double cone (DC), outside diameter of each winding 110 mm, angle between windings 100°
Chapter 4. Longitudinal study of recovery arm and hand, first 13 patients remaining 8 patients	Digitimer D190, max. output 1.5 Tesla. Magstim 200, max. output 2.0 Tesla	Double cone (DC), outside diameter of each winding 142 mm, angle between windings 100° DC outside diameter of each winding 110 mm, angle between windings 100°
Chapter 5. Ipsilateral responses in normal subjects	Magstim 200, max. output 1.5 Tesla	DC outside diameter of each winding 110 mm, angle between windings 100°. SB outside diameter of each winding: 75mm.
Chapter 6. Effect of voluntary contraction on proximal and distal muscles. Effect of increasing stimulus intensity on motor unit firing probability.	Magstim 200, max. output 2.0 Tesla	DC outside diameter of each winding 110 mm, angle between windings 100°

2.7 Data analysis

CED SIGAVG software was used to analyse the data. Background EMG levels, response amplitudes, onset latencies and response durations were determined.

2.7.1 Measurement of background EMG and MVC

Background EMG levels were extracted from records sampled two seconds after each cortical stimulus. This ensured that these levels were assessed at a time when they could not have been influenced by the magnetic stimulus. Averages of 10-40 sweeps (the number varied for each study) for all sampled periods of background activity were compiled and the mean voltage level of background EMG was determined from this average.

The maximal voluntary contraction (MVC) sweeps were averaged in the same way, but care was taken to make sure that no sweeps that contained efforts that were below maximum were included.

2.7.2 Criteria for the presence of a response to TMS and determination of response thresholds.

The criterion for the presence of an EMG response to TMS was a peak occurring within the normal range of latencies for the muscle (see Rothwell, Thompson, Day Boyd and Marsden, 1991) or at up to 50 ms after the stimulus. Such a peak had to be present in response to at least 3 of the 10 stimuli given. The peak had to be more than twice the mean level of background EMG, and larger than other peaks in the background.

Ipsilateral responses were identified using the same relative peak size and latency criteria that were defined for the contralateral responses.

The lowest stimulus intensities needed to produce an EMG response in each muscle, first in the relaxed state (passive threshold) and then with a gentle background contraction (active threshold), were determined at the beginning of each test. These thresholds (expressed as percentages of the maximum output of the stimulator) were

defined as the minimum stimulus intensity at which a contralateral EMG response was obtained in approximately half of the trials.

2.7.3 Peak Amplitude.

The peak amplitude was measured from the highest peak in the rectified EMG response, regardless of whether it was the first component or a subsequent peak. This measure has proved to yield comparable results to the mean peak area (Flament et al., 1993). The mean peak amplitude was taken by logging the peak amplitude from responses in single sweeps and calculating the mean on a spreadsheet. A quick check was also obtained by the creation of an average sweep by use of the SIGAVG programme, but this method gave a conservative estimate because there was some variation in the timing of the peak response amplitudes. The first stimulus often produced a particularly large response (Hall, 1990). To prevent the effects of this large response from biasing the results, the first response from each new block of stimuli was routinely eliminated from the analysis.

Absolute EMG response amplitudes from different muscles, subjects or recording sessions cannot be readily compared. Differences in skin resistance, amount of fat between electrodes and muscle and the differences in electrode placement all contribute to the variation in EMG recordings. In addition to all these variables response amplitudes are dependent on the background level of EMG (Hess, Mills and Murray, 1987).

The response amplitudes need to be expressed in relative terms to allow comparison. Therefore mean peak response amplitudes were normalised to mean background EMG levels $(\frac{Peak - Background}{Background})$. The normalised amplitude of responses were related to different characteristics depending upon the focus of each study. For example, to allow comparison of response size between tasks the normalised response amplitudes for the complex tasks, i.e. pincer, power and rotation, were expressed as a percentage of the value obtained for the abduction task.

2.7.4 Response latencies.

Onset latencies of EMG responses were measured from the onset of the stimulus artifact to the first departure from the background EMG at the beginning of the response. This time includes both the central and peripheral motor conduction times. The peripheral motor conduction time in particular is dependent on the size of the individual, so latencies vary not only between muscles but also between individual subjects. Some authors have chosen to measure central motor conduction time (CMCT); this is normally derived by subtracting the peripheral conduction time from the onset latency of the response to TMS (see Rothwell et al., 1991; Heald et al., 1993a). The peripheral conduction time is usually measured from responses to magnetic stimulation with the coil held over the spine at the low cervical level. However, because of doubts as to the exact site of stimulation of magnetic stimulation at both the cortical and at the spinal levels (Edgley et al., 1990; Burke, et al., 1993; Davey et al., 1994), and the large range of values exhibited by normal subjects (Heald et al., 1993a), it is not clear which central processes the CMCT actually represents. In any case when analysing patients data we, like others, compared results from the affected side with those obtained from the unaffected limb (Thompson et al., 1987; Hömberg et al., 1991).

Within subjects response latencies are much more consistent than response amplitudes. They were therefore an important indicator of change in the longitudinal study. Voluntary contraction facilitates responses to TMS and decreases onset latencies by approximately 3ms. However in the presence of a little background voluntary contraction response latencies are remarkably constant (Hess, Mills and Murray, 1987; ischka et al., 1993). Because of their consistency, response latencies have been taken from averages compiled from all responses within a block. This approach biases the onset latency measurement to the shortest latency responses in the average.

2.7.5 Response duration.

The end of excitatory responses to TMS are very clear because they are usually followed by a period of EMG suppression (Fuhr, Agostino and Hallett, 1991; Roick, von Giesen and Benecke, 1993). Response durations were measured from single sweeps. The median value was chosen to represent response duration for each condition.

2.8 Pilot tests to investigate whether task dependent responses could be obtained using the DC coil.

2.8.1 Experimental Procedure

Two young subjects (CD and DF; aged 20 and 35), were tested using the DC coil. One of them (DF) had participated in the original study of Flament et al. (1993).

Surface EMGs were recorded from first dorsal interosseous (1DI) of both hands for DF and from the preferred right hand for CD. The subject was asked to produce isometric abduction of the index finger and several MVCs were recorded. The active thresholds in 1DI were determined while the subject performed the abduction task at 5% MVC. The stimulus intensity was then adjusted relative to the threshold values. Subject DF was tested at the level of intensity that had proved to be most effective with the circular coil (i.e. at active threshold + 6-8% max. output of stimulator; max = 1.5 Tesla). Subject CD was tested at 2% and 6% max. output above the active threshold while she performed the tasks with her dominant right hand. Twenty five magnetic stimuli were delivered pseudorandomly at a mean interval of 4 s, during the performance of each task. In order to keep the data collection time to a minimum the tasks were carried out in blocks, starting with abduction. To confirm the reproducibility of the results, abduction was repeated after completing the other tasks. The power task was not included in CD's test.

2.8.2 Data Analysis

Both single sweep and averaged EMG responses were measured for each task. Mean peak response amplitudes and mean background EMG levels were extracted to calculate normalised response amplitude ($\frac{Peak - Background}{Background}$).

To allow comparison of response size between tasks the normalised response amplitudes for the complex tasks, i.e. pincer, power and rotation, were expressed as a percentage of the value obtained for the index finger abduction task. For each hand or stimulus intensity the student's t-test (two tailed) was used to compare peak amplitudes of responses in single sweeps obtained in the complex tasks vs. the simple abduction task.

2.8.3 Results

Responses obtained during the pincer task were significantly larger than abduction responses at both stimulus intensities (22% and 26%) in CD (figure 2.2A). Responses during rotation were larger than abduction when the near threshold stimulus strength was used, but smaller than abduction when the higher intensity was employed. Neither of these rotation results reached statistical significance.

When he used his preferred right hand, DF had larger responses for all of the complex tasks, but only rotation responses were significantly greater than abduction (Figure 2.2B).

In every subject that Flament et al. (1993) tested with the circular coil, responses recorded during at least one complex task were larger than during abduction. The two subjects tested with the DC coil, with stimulation set at 6-8% above active threshold, displayed the same degree of task dependency when using their preferred hand. In CD's case the task dependency is apparently better during tests using lower stimulation intensities.

Flament et al. (1993) did not include the non-dominant hand in their tests. In the one subject tested here, all complex tasks performed with the non-preferred hand were

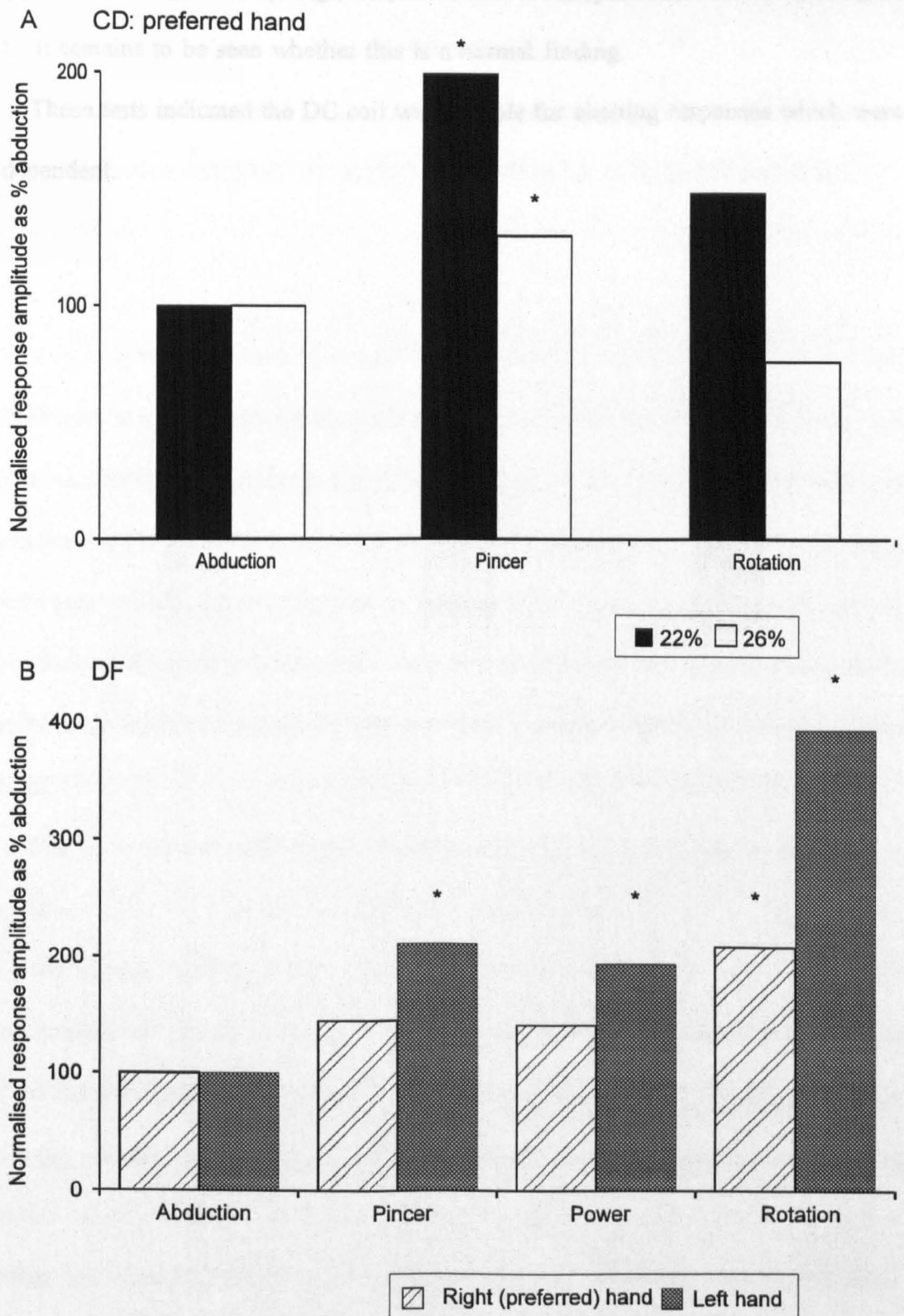


Figure 2.2 Task dependent responses in 1DI obtained using the DC coil.
Average of 25 1DI response amplitudes normalised to baseline EMG level, expressed as a percentage of the response in abduction (100%).
An asterisk denotes statistically significant difference from abduction value ($p < 0.05$, two tail t-test)

accompanied with significantly larger responses than the simple abduction task (see figure 2.2B). It remains to be seen whether this is a normal finding.

These tests indicated the DC coil was suitable for eliciting responses which were task dependent.

CHAPTER THREE.

THE LACK OF TASK DEPENDENCE IN EMG RESPONSES IN FIRST DORSAL INTEROSSEOUS MUSCLE TO TMS IN STROKE PATIENTS.

3.1 Summary

In young healthy adults, the amplitude of short-latency EMG responses to TMS in hand muscles is larger during the performance of different isometric hand grips than during a non-functional abduction task (Flament et al. 1993). There is good evidence to suggest that the CS system is involved in the execution of these tasks and that it mediates the responses to TMS. I have investigated whether differential responses to TMS during performance of different gripping tasks were also present in a group of ten older adult controls and in eight stroke patients who exhibited a variable degree of recovered hand function.

The older normal subjects did not show such clear task dependency as found in young adults. Only two subjects had larger responses during a "complex" grip task than during the "simple" abduction task. Task-related variation in response may be an effect of skill practice or an effect of age. Young stroke patients, whose hand function was impaired did not show the strong pattern of task variation that was normal for their age, when using the affected hand. Only a particularly well recovered patient had normal task dependent responses. The older patients using the affected hand also showed a lack of responses that were larger for the "complex tasks" than those recorded during abduction. However two of them had very substantial responses during the rotation task when using the unaffected side. The increased use of the unaffected hand forced on patients for many weeks and months after stroke may have caused some reorganisation of the healthy, but aged hemisphere.

The patients were also tested with a focal magnetic coil to investigate the possibility that the intact (ipsilateral) cortex was contributing to their recovered hand movement. No ipsilateral responses were observed.

3.2 Introduction

There is a substantial body of evidence to suggest that, in man and other primates, the capacity to perform skilled, independent finger movements depends upon the integrity of the CST, and particularly upon its direct, CM component. This evidence has come from anatomical, electrophysiological and lesion studies (Schoen, 1964; Lawrence and Kuypers, 1968a; Kuypers, 1981; Palmer and Ashby, 1992; Porter and Lemon, 1993) as well as from a consideration of the comparative anatomy and development of different species (Heffner and Masterton, 1975; 1983; Armand, 1982; Flament, Hall and Lemon, 1992; Lemon, 1993a). In monkeys and baboons it has been demonstrated that a single hand muscle is represented over a wide cortical area (Lemon, 1988; Lemon, 1990; Donoghue, Leibovic and Sanes, 1992) and that individual CM cells may facilitate activity in a number of different hand muscles, presumably via the branching of their axons within the spinal grey matter (Shinoda, et al., 1981; Lawrence et al., 1985; Buys et al., 1986). If CM cells were recruited in a task-specific pattern, i.e. a given CM cell was recruited when a task demanded the contribution of the specific functional group of muscles that were facilitated by that CM cell, then this might explain the apparent redundancy in the large number of different CM cells that project to the motoneurons of one muscle (Lemon, 1993a).

In young healthy volunteers, Flament et al. (1993) showed that the amplitude of responses to magnetic stimulation recorded from an intrinsic hand muscle (first dorsal interosseous, 1DI) varied according to the task being performed. Clear, consistent and statistically significant changes in response amplitude were observed, being particularly striking for the pincer and rotatory grips (see figure 3.1).

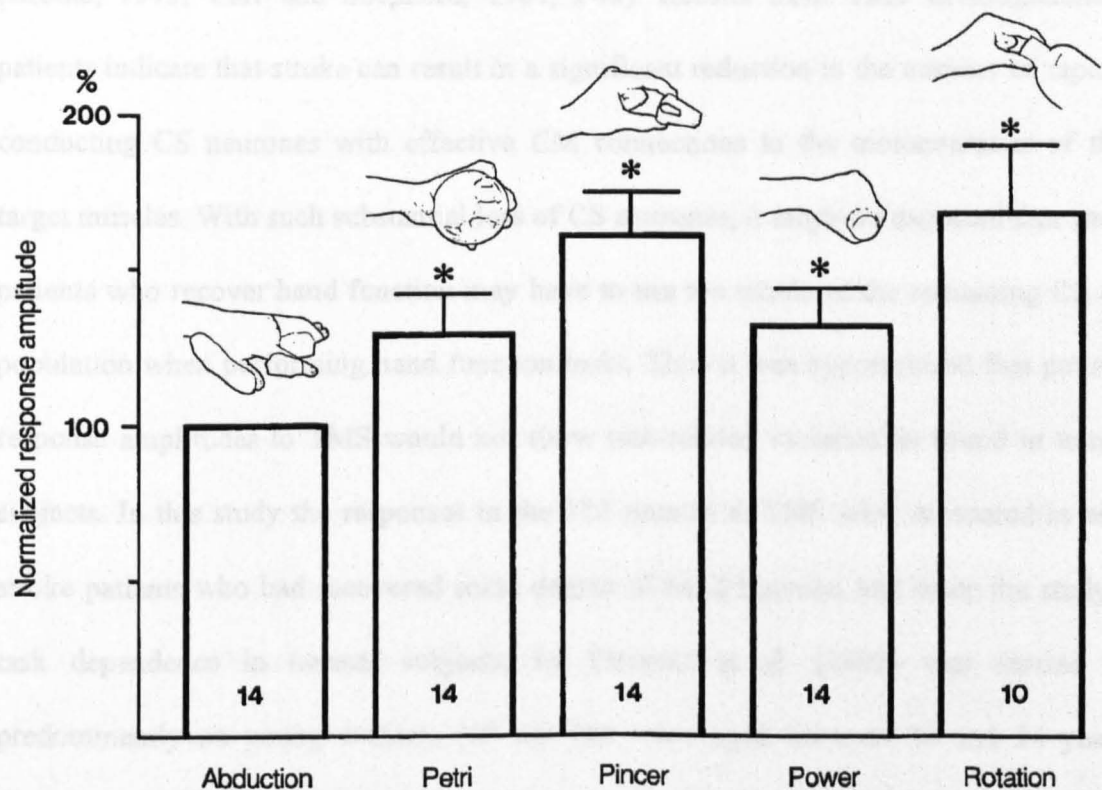


Figure 3.1 Results from Flament et al (1993)

Mean (\pm SEM) 1DI response amplitudes normalised to baseline EMG levels for all subjects, expressed in abduction (100%). An asterisk denotes statistically significant difference from abduction value (paired t-test). The numbers in each bar denote the number of subjects in which the task was tested.

Flament et al. (1993) suggested that this variation might be due to the activation, by the TMS, of different sub-populations of CM cells during different tasks, as described above.

Even if they recover, stroke patients suffering from a unilateral hemiparesis, often appear slow and clumsy when using the affected hand. They sometimes have trouble in positioning their thumb and fingers for precision and for maintaining grip pressure (Brodal, 1973; Carr and Shepherd, 1987, P48). Results from TMS investigations of patients indicate that stroke can result in a significant reduction in the number of rapidly-conducting CS neurones with effective CM connections to the motoneurones of their target muscles. With such substantial loss of CS neurones, it might be expected that stroke patients who recover hand function may have to use the whole of the remaining CS cell population when performing hand function tasks. Thus it was hypothesised that patients' response amplitudes to TMS would not show task-related variation as found in normal subjects. In this study the responses in the 1DI muscle to TMS were measured in eight stroke patients who had recovered some degree of hand function and since the study of task dependence in normal subjects, by Flament et al. (1993) was carried out predominantly on young students (all but two were aged between 20 and 24 years), additional normative data was collected from a group of normal subjects whose ages more closely matched the stroke patients.

To investigate whether the undamaged hemisphere could be contributing to their recovered hand movement, the patients were also tested for responses in the affected side 1DI to magnetic stimulation of the ipsilateral cortex.

3.3 Methods.

3.3.1 Patients and aged matched normal subjects

Eight stroke patients, seven male and one female, aged 22 to 69 years were investigated. The patients had all been treated in the Occupational Therapy Department

at Addenbrooke's Hospital, Cambridge where detailed records of their presentation after stroke and of their recovery had been kept. Seven of them had CT scans indicating striatocapsular lesions. The remaining patient (RB) was not scanned. His symptoms were purely motor with no apparent sensory or cognitive impairments, suggesting that his stroke was also caused by a small lesion in the internal capsule (Allen, 1984). Immediately after stroke, all eight patients had little or no upper limb movement and no function in the affected hand. Table 3.1 gives the details of the patients' ages and side affected and duration since stroke at the time of this study.

The first five patients were recruited to the investigation having already recovered hand function to various degrees. They were between eight months and ten years post stroke. Those of working age had returned to full time employment and RB, a retired farmer, had recovered sufficiently to look after his pigs. They all used their affected hands for bimanual tasks, e.g. for holding and carrying things, driving, eating and other usual daily living tasks, but not for tasks requiring fine control, such as writing. AP, a bank teller, used her affected hand most constantly when counting banknotes at work. WH was still receiving Occupational Therapy to improve his hand function. At home he was able to use his affected hand to a limited extent. He could do simple things such as switching on lights or picking up small light objects, but he was unable to lift a cup to drink using the affected hand, or to use a knife for cutting up food.

The remaining three patients were selected from the longitudinal study, so that some history of their responses to TMS prior to recovery of their hand function was available, and their progress was followed for up to one year after stroke (see chapter 4). The first of these three patients, CS, had small late responses to TMS in 1DI even at three days after stroke, when he was unable to activate the muscle voluntarily. He made an early and rapid recovery and was tested for task dependency of responses at two weeks, when recovery of hand function was considered to be sufficient for the tasks used in the

Table 3.1. Patient's characteristics.

Patient	sex	age	affected hand	Time after stroke	Peg test time (s)		Nuts/ bolts time (s)		Power grip (affected/unaffected**)	Pinch grip
					affected	unaffected**	affected	unaffected**		
WH	m	68	right*	8 mths	41	15	unable	no test	0.14	no reading
BH	m	52	left	13 mths	11***	9	26	11	no test	0.89***
GJ	m	36	left*	10 yrs	16	10	36	19	0.70	0.57
RB	m	65	right	7 yrs	17***	13	25	22	1.00***	1.09***
AP	f	34	right*	8 yrs	12	10	25	19	0.88***	0.78***
CS	m	22	right*	2 wks	17	9	51	16	0.47	0.44
SO	m	37	right*	6 mths	44	11	unable	no test	0.21	0.43
DF	m	69	right*	1 yr	33	12	unable	no test	0.15	no reading
mean (s.d) normal times for the peg and nuts/bolts tests and normal variation between hands for grip strength					preferred 10.4 (1.26)	non-preferred 11.0 (1.45)	preferred 15.7 (4.70)	non-preferred 19.5 (3.60)	±0.06 (0.08)	±0.08 (0.23)

* Preferred hand before stroke

** Performance of the patients' unaffected hands on these tests was within the normal range for their age and sex. The peg test and nuts/bolts test are timed so scores over 1 indicate a longer performance time for the affected side. Grip strengths below 1 indicate affected hand than is weaker than the unaffected hand. Patients who were unable to obtain a reading for pinch grip, were able to form hand shape for grip, but were unable to exert pressure on guage. The normal peg and nuts/bolts times and grip strength variation between hands given are for a 50 year old male, all test scores are age dependent, normal performance times increase with age and grip strength decreases..

*** Test score for patient's affected hand was within normal range.

investigation. He was able to return to work as a motor mechanic within six months of the stroke. The other two patients (SO and DF) recovered more slowly. Neither had voluntary activity or responses to TMS in 1DI in tests at two, six and twelve weeks after stroke. Responses and activity were first apparent at their six month test. SO was investigated for task dependent responses at six months and DF was investigated at twelve months. A year after stroke SO returned to work as an electrical engineer and DF, although retired, was able to resume his activities as a city guide and community education tutor.

In addition to motor impairment, GJ had sensory loss after stroke and AP was initially dysphasic, but this had largely resolved within three months of stroke. At the time of the test no language problems were evident. No perceptual or other higher cognitive deficits were found in any of the patients during the course of their Occupational Therapy treatment in earlier weeks and months.

Hand function at the time of the study was assessed using the tests described in chapter 2, section 2.2.

Ten normal subjects, five of them male, aged between 43 and 60 years, (mean age 54 years) participated. Nine of them were right handed.

3.3.2 Experimental Procedure

Surface EMGs were recorded in patients from first dorsal interosseous (1DI), abductor pollicis brevis (AbPB), abductor digiti minimi (AbDM) and extensor digitorum communis (EDC) on both sides. At the beginning of each session, the EMG activity from all four muscles during the execution of the different tasks with one hand and then the other was recorded. The patient first practised each task using the unaffected hand to ensure that he/she understood the task before attempting to perform it with the affected hand. The patient was asked to maintain each grip for around three seconds and to relax in between trials. Five to ten trials of each task were recorded with either a DTR tape or

a chart recorder.

For comparison with the patient EMG recordings during the tasks, two of the normal subjects had surface EMGs recorded from the same muscles on both sides. In the remaining normal subjects EMGs were recorded from left and right 1DIs only.

In patients, the damaged hemisphere was tested first with TMS, while the affected hand was used to carry out the tasks. In normal subjects the non-preferred hand was tested first. The subject (i.e. normal or patient) was asked to perform the abduction task and to maintain a stable level of EMG in 1DI at 5% of MVC. While performing this task, the intensity of the TMS was slowly increased until responses were obtained to about half the stimuli delivered. Stimulus intensity was then adjusted to around 8% of max. stimulator output above this threshold value. The intensity was adjusted if this stimulus strength yielded responses that were either near supramaximal or very small with respect to the background EMG. Stimulus intensities of 6-8% above threshold had been found to be optimal for producing task-related differentiation of EMG responses in young normal subjects (Flament et al., 1993). Twenty five stimuli were delivered while the subject performed each task. The stimuli were delivered pseudorandomly at a mean interval of four seconds. In order to keep the data collection time to a minimum the tasks were carried out in blocks, in the following order: abduction, pincer, power, rotation. Abduction was then repeated to confirm the reproducibility of the results. Three patients (CS, SO and DF) did not perform the power task.

The coil was repositioned for the optimum response from the other hand and the threshold stimulus strength was noted. For normal subjects the stimulation intensity was set at around the active threshold + 8% max. output of stimulator, as it had been for the first hand. For patients the intensity was changed until the mean peak amplitude of the responses recorded from the unaffected hand in abduction matched those found in the affected hand. This was done to compensate for the patient's weakness. However in the

more severely affected patients, matching amplitudes proved to be impossible. Even the threshold responses on the unaffected side were larger than the responses obtained at 8% above threshold from the affected side. Because of this, the intensities used for WH and SO were matched relative to threshold; for example, both affected and unaffected side were tested at 6% max output above their respective active thresholds. In patients whose affected and unaffected hands were tested at markedly different intensities (5 out of 8 patients), an additional block of abduction trials were performed by the unaffected hand with the intensity set to the level used for the affected hand.

3.3.3 Investigation of Responses to Stimulation of the Ipsilateral Hemisphere.

To test for ipsilateral responses, four of the patients (WH, GJ, RB and AP), were tested with a small butterfly coil (SB, 70 mm coil). The coil was hand-held over a point 6 cm lateral to the vertex and stimuli that were strong enough to produce supramaximal responses in the contralateral hand (35-80% of max. stimulator output) were delivered while the patient abducted both index fingers simultaneously. The coil was positioned to stimulate each hemisphere in turn.

The remaining three patients CS, SO and DF were tested for ipsilateral responses as part of the longitudinal study (see chapter 4).

3.3.4 Data Analysis

Mean peak response amplitudes and mean background EMG levels were extracted to calculate normalised response amplitudes $\left(\frac{Peak - Background}{Background} \right)$ for each task and each hand. This served to compensate for any slight variation in the background EMG from one task to another, since sometimes patients had difficulty in maintaining constant background EMG levels throughout the experiment.

The mean normalised response amplitudes for the complex tasks, i.e. pincer, power and rotation, were expressed as a percentage of the value obtained for the index finger abduction task. For each hand of each subject, the student's t-test (two tailed) was used

to test for differences between response peak amplitude obtained in the complex tasks vs. the simple abduction task. Analysis of variance (single factor) was performed to compare the pooled normalised response amplitudes across tasks in normal subjects. Mean latencies and the median duration of the responses were also measured.

3.3.5 Cross correlation procedures

EMG recordings of task performances from the affected and unaffected side 1DIs, without TMS, were transferred from DTR tape to PC using Cambridge Electronic Design Spike2 software. Lengths of EMG data were chosen from the three second periods of activity when the patient was performing each task. A custom written analog cross correlation program was used to assess short-term synchrony between the two 1DI EMGs.

3.4 Results

3.4.1 Assessment of Hand Function in the Patients

Table 3.1 (page 71) lists the patients' performance on hand function tests carried out on the same day as the TMS. For all eight patients performance on these tests with the unaffected hand was within normal limits for age-matched healthy subjects. As a group the proficiency of their hand function on the affected side varied.

WH, CS, and SO had their hand function tested again at one year post stroke. All three had improved but only CS reached near normal performance (see table 3.2).

Table 3.2 Recovering patients' hand function test scores at one year after stroke.

Patient	Peg test time (s)		Nuts/bolts time (s)		Power affected/unaffected**	Pinch grip
	affected	unaffected**	affected	unaffected**		
WH	23	15	49	24	0.54	0.89***
CS	12	10	23	19	1.06***	1.16***
SO	28	10	108	18	0.38	0.71***

** and *** see legend for table 3.1

3.4.2 Pattern of EMG Activity during Task Performance

EMG records were examined for differences between tasks and between hands. The relative amounts of activity in the four muscles sampled varied according to the task being performed. In the normal subjects and in the unaffected hands of some of the stroke patients' unaffected hands the 1DI activity was not completely isolated during the 1DI task (see figure 3.2 and 3.4). It was accompanied by lesser degrees of activity in AbPB and EDC. The bursts of activity were quite distinct in all the tasks, with quiet episodes in the recordings between contractions.

When they used the affected hand, all the patients modulated the balance of muscle activity across tasks, but the pattern of activity was not always the same as seen in the unaffected hand; some patients showed increased activity in one or more of the synergists. This may have been due to greater weakness in 1DI, or to slight variations in the posture of the hand around the objects. Examples from a patient are given in figure 3.3. This patient (SO) was able to activate the 1DI with minimal activity of the other muscles when abducting the index finger of the unaffected hand, so the inability to avoid co-contraction of 1DI with the other tested muscles when using the affected hand was particularly striking.

Four patients, BH, WH, CS and DF showed interesting mirror effects when performing the tasks with their affected hands: involuntary activity of the unaffected hand was observed. Examination of the their EMG recordings showed that activity in homologous muscles was highly synchronised across the two sides during task performance. Examples from DF and BH of mirrored 1DI activity in the unaffected hand during abduction of the affected side index finger are given in figure 3.4. Cross-correlations of the activity between right and left 1DIs were carried out for CS, DF and WH, but no outstanding peaks were found to suggest that the motoneurones supplying the two muscles received a common input. No mirroring in the EMG was evident during the

tasks when using the unaffected hand. Mirroring was not present in the EMG records of the other patients or in the normal subjects.

A further investigation of normal subjects and stroke patients' independent finger movement and mirroring of finger movement measured using electrogoniometers is reported in the Appendix.

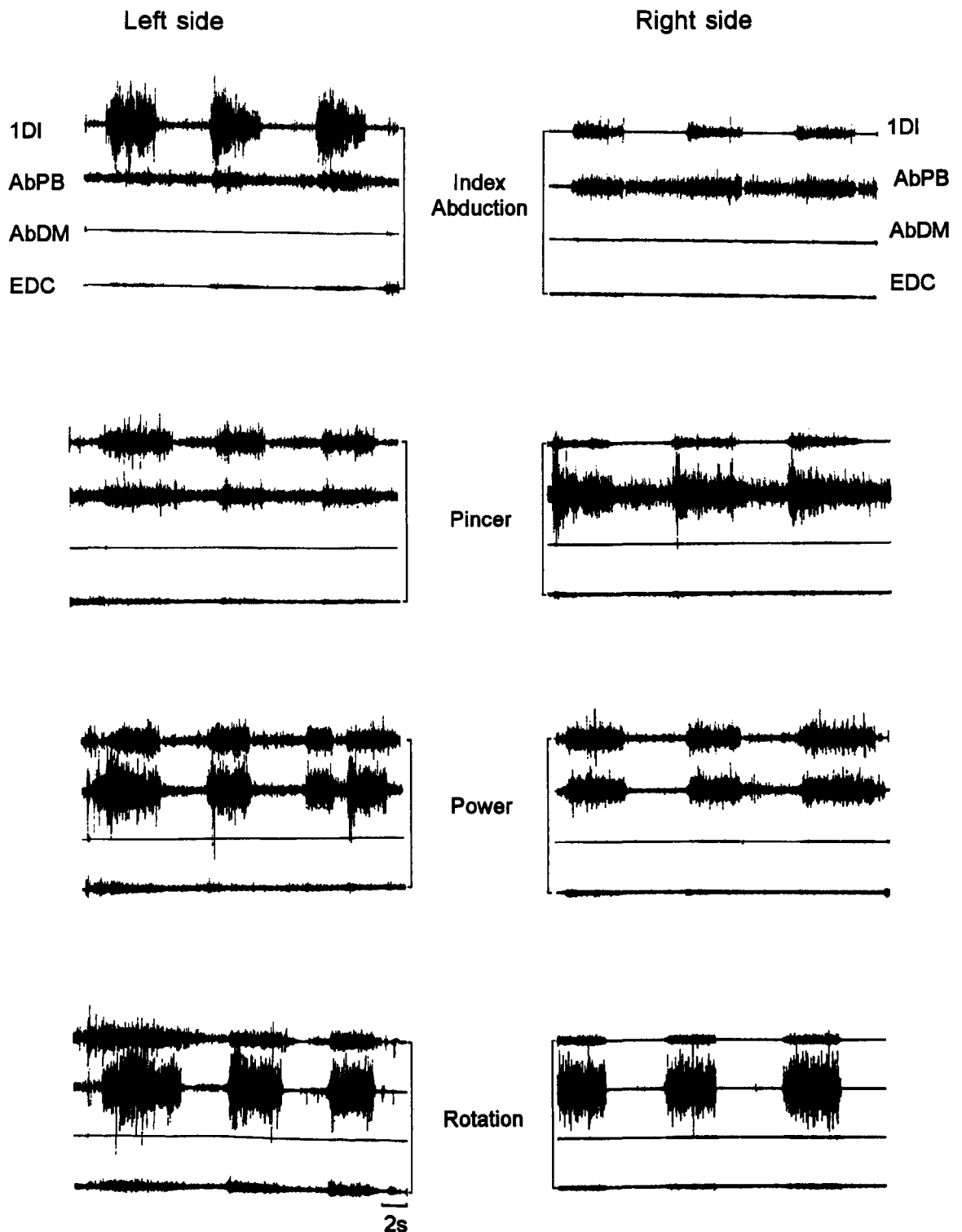


Figure 3.2 EMG activity recorded during tasks performed by a normal subject

EMG activity recorded from four hand and forearm muscles during tasks performed by a normal subject. The subject was required to perform the different isometric tasks for about four seconds and then to relax between trials. Three trials are shown for each task. Note that during index finger abduction some activity, although weakly modulated, is present in AbPB as well as that in 1DI. Gains are the same for left and right sides. Abbreviations: 1DI, first dorsal interosseous; AbPB abductor pollicis brevis; AbDM, abductor digitis minimi; EDC, extensor digitorum communis.

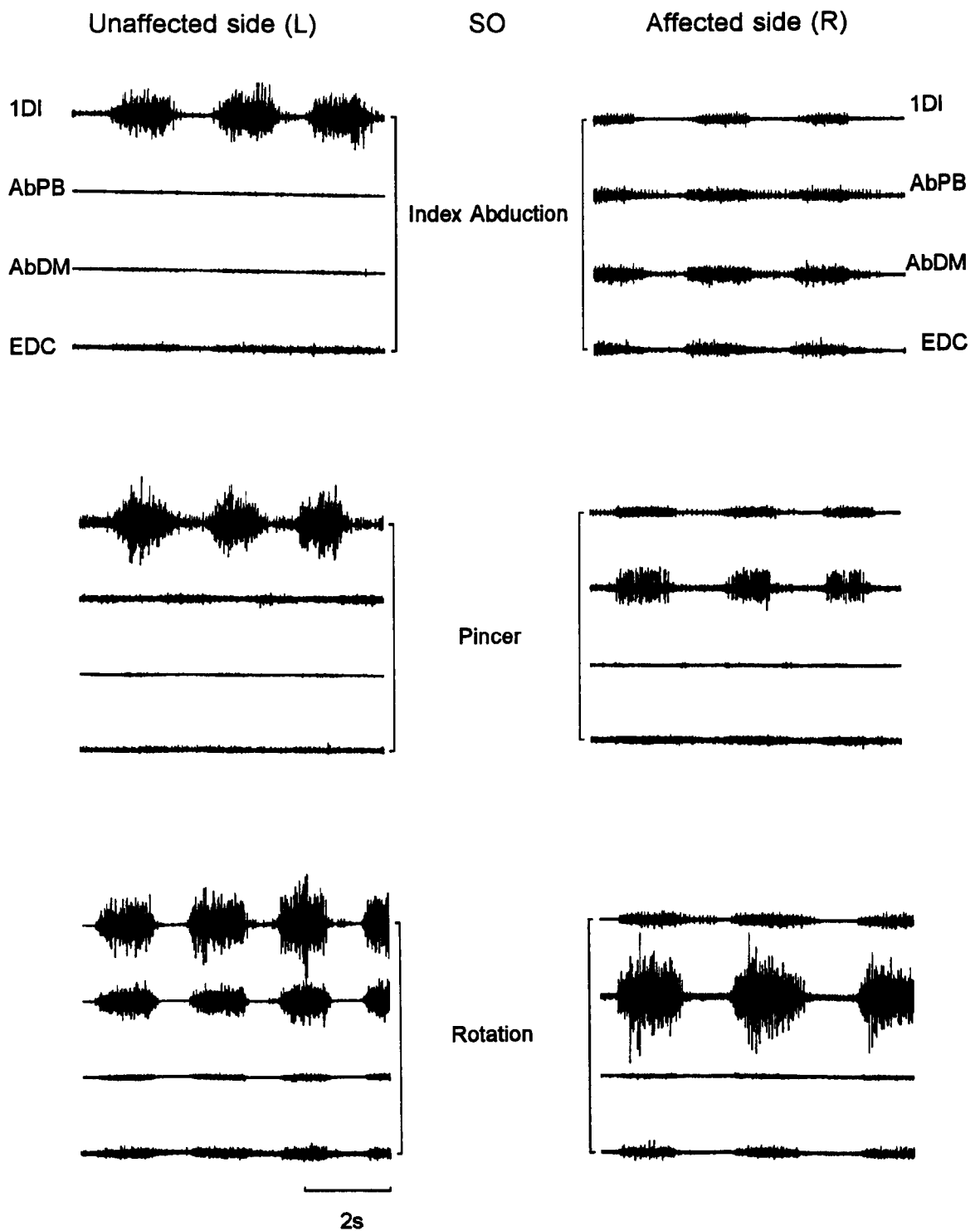


Figure 3.3 EMG activity recorded during performance of abduction, pincer and rotation tasks in patient SO

Three trials are shown for each task. Comparison of activity between the two sides shows increased contribution of muscles other than 1DI on affected side. Gain on the affected side is twice that of the unaffected side.

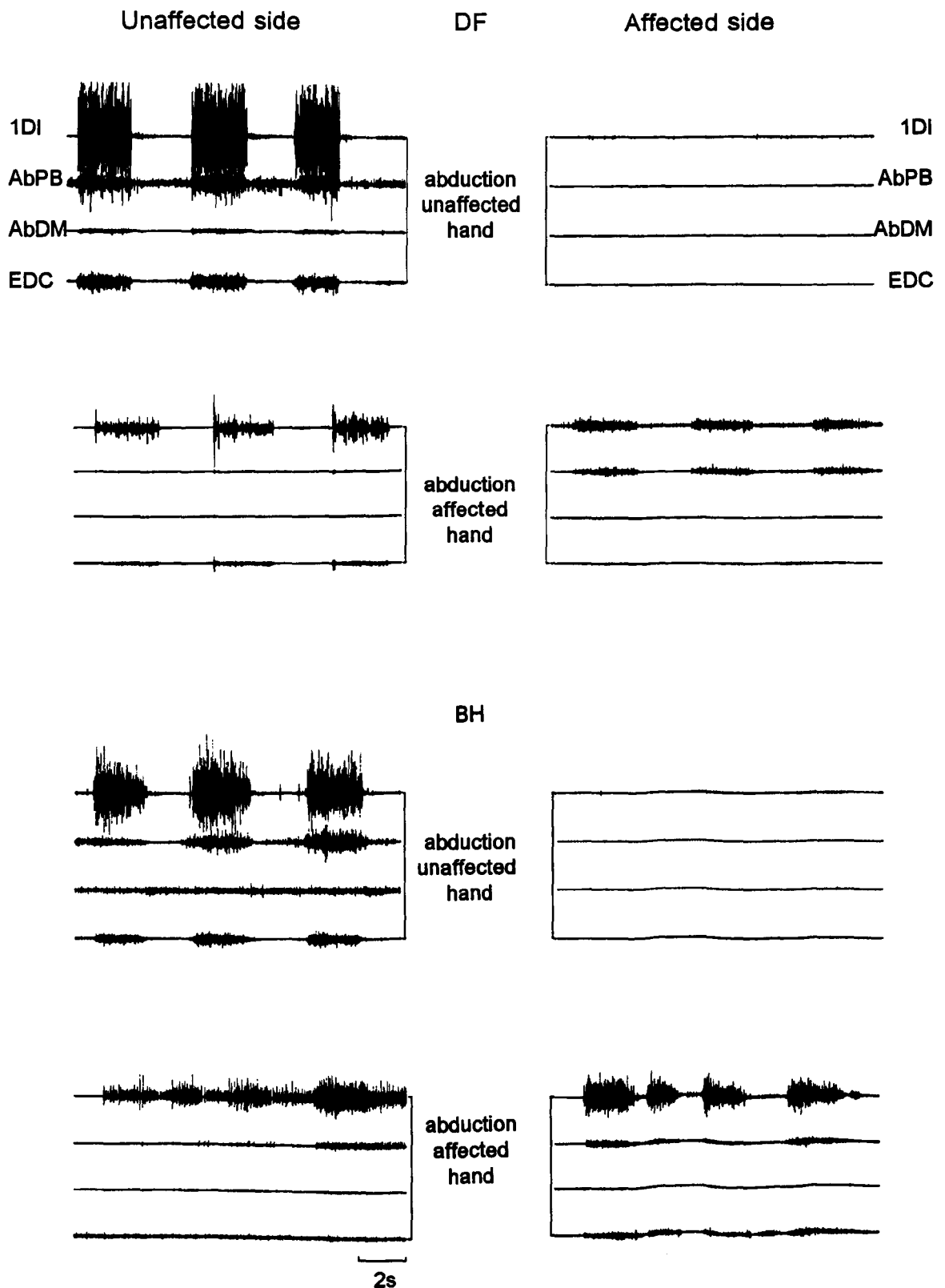


Figure 3.4 Mirror EMG activity in two patients

EMG activity recorded from both hands during index finger abduction performed with the unaffected hand (top traces) and the affected hand (bottom traces). When the task is performed with the affected hand, EMG activity is seen in the unaffected muscles. Gains are the same for unaffected and affected sides.

3.4.3 Comparison of MVC and response characteristics between hands.

MVC

Comparing MVC as measured by EMG is subject to variations due to differences in skin conductivity, positioning of electrodes etc (see chapter 2, section 2.7.3.). However such a comparison may be acceptable for giving a broad indication of difference between sides. The difference in MVC of 1DI between hands in normal subjects was within 30%, the MVC was not always greater on the preferred side. The patients MVC ratios between affected and unaffected hand did not match perfectly with their hand function test results but the three patients who were most severely affected at the time of the tests had the lowest MVC ratios, (WH, SO and DF; see table 3.3).

Threshold intensities.

The difference between the threshold stimulus intensities required to produce a response in the voluntarily contracted 1DI of the two hands while performing the abduction task were within 5% (max. output of stimulator) in all but one of the normal subjects. In contrast to previous findings (Triggs, Calvanio, Macdonell, Cros and Chiappa, 1994), there was no clear effect of hand preference. Three subjects had higher thresholds for obtaining a response from 1DI on the preferred side. In all but two of the patients, higher intensities were needed to obtain responses from the affected side (see table 3.3). The two patients who, contrary to expectation, had substantially lower thresholds for responses in the affected hand, had both made good recoveries from strokes that happened many years prior to the test. These patients were considerably younger at the onset of stroke than others who were tested years after stroke.

Onset latencies and durations.

Mean onset latencies for both preferred and non-preferred hands in normal subjects were similar to those found previously in normal subjects (Flament et al., 1993) and the difference between hands was negligible and not consistently longer or shorter for the

Table 3.3. Patient's MVC and response characteristics for affected and unaffected 1DI.

Patient	1DI mvc aff/unaff(%)	Active threshold		Latency		Duration	
		affected	unaffected	affected	unaffected	affected	unaffected
WH*	13	55	50	28.5	23.3	8.3	8.3
BH*	17	55	50	27.0	24.0	19.0	14.0
GJ*	95	50	60	25.0	25.0	24.0	11.3
RB*	45	50	40	30.0	27.0	17.0	10.8
AP*	145	32	42	19.0	19.5	11.0	8.1
CS**	136	45	37	24.8	23.0	22.0	14.3
SO***	11	26	24	35.8	24.0	8.1	13.0
DF***	9	30	26	28.3	25.0	28.3	13.3

normal difference between sides within:

	MVC	Active threshold	Latency (ms)	Duration (ms)
	30%	**5%	1.75	4.4
(n=)	(9)	(9)	(7)	(7)

* tested with round coil, 1.5T stimulator

** tested with DC coil, 1.5T stimulator

*** tested with DC coil, 2T stimulator

Active threshold is expressed as % max. output stimulator.

preferred hand across subjects (mean (s.d) preferred hand 21.7, (1.5) ms, non-preferred 22.3, (1.6) ms). The latencies of responses on the patients' unaffected side were within 2 s.d. of the normal mean in all but one case. The exception, RB, was a remarkably tall man, his unaffected response latency of 27 ms may be explained by his height and longer arm length. On the affected side five patients had response latencies that were longer than normal. Their response latencies were 3 ms or more than 3 ms longer on the affected side than the unaffected side. The three patients with normal response latencies included a well recovered patient AP and a patient who went on to recover well, CS. However at the time of the test CS and the last of the three, GJ, were not near to normal in hand function.

The normal subjects' median response durations were pooled to find an average response duration for preferred and non-preferred hands. Preferred hand mean response duration was 10.8 ms, non-preferred response duration was a little longer at 13.1 ms. However there was no consistent difference between sides across subjects. Within individual subjects the difference ranged from 0.5 ms up to 4.4 ms. The median durations of the patients unaffected side responses were normal. In five patients the response durations on the affected side were 5 ms or more than on the unaffected side. The long response durations were not related to the size of the response since in some patients the affected side responses were much smaller than on the unaffected side.

3.4.4 Comparison of response amplitudes recorded during performance of different tasks.

The target level for background EMG activity during performance of the four tasks was 5% MVC; the actual values recorded ranged from 5% to 15% in the normal subjects and from 5% up to 22% of MVC in the patients. However across tasks for each hand the normal subjects and the patients who were more than one year post stroke managed to maintain constant background EMG levels; variation was less than 3% MVC. The four patients who were tested earlier in their recovery had a little more difficulty in keeping

EMG levels stable when using the affected hand, but even they kept within 6% MVC across tasks. Three of them had lower activity levels (%MVC) during abduction.

Normal subjects

Table 3.4a) gives the normalised response amplitudes in 1DI across tasks for the normal subjects expressed as a percentage of the response recorded during index finger abduction. In contrast to the results of Flament et al. (1993), who tested young adult subjects, only two out of ten of the older normal subjects in this study, had significantly larger responses during a complex task than during the abduction task when using the preferred hand. Five subjects had significantly smaller responses in complex tasks, particularly in pincer and power, than during abduction. The results were similar for the non-preferred hand, two out of nine subjects had larger responses in a complex task than during abduction, three had responses during complex tasks that were significantly smaller. When the results of the normal subjects were pooled there were no significant differences in the normalised response amplitudes found between any of the tasks, for either hand (Single factor ANOVA). The results are shown graphically in figure 3.5.

The lack of large responses during complex tasks was a rather surprising result, given the strong pattern found by Flament et al. (1993), in which every young subject had at least one task with responses larger than abduction, and half of them had large responses in all complex tasks. Therefore as a check that the results in older subjects were not due to use of the DC coil, one of the subjects was retested with the round coil, as used by Flament et al. However there were still no large responses found for the complex tasks (see table 3.4 b).

Table 3.4 Normalised response amplitudes for complex tasks expressed as % abduction.

a) Normal older subjects

Subject	Preferred hand				Non-preferred hand			
	intensity	Pincer	Power	Rotation	intensity	Pincer	Power	Rotation
1	T+10	82	93	89.5	T+10	*220	129	*184
2	T+10	94	104	108	T+10	166	125	96
3	T+8	*61	*55	80	T+11	146	106	148
4	T+8	124	131	*167	T+9	101	115	*65
5	T+8	*152	not tested	90	not tested			
6	T+7	89	*59	80	T+6	88	84	105
7	T+7	*55	*47	129	T+6	91	*48	69
8	T+4	*48	*70	130	T+6	*56	102	99
9	T+8	82	87	92	T+8	101	65	*140
10	T+5	*70	62	*44	T+7	60	37	*43
mean		85.7	78.7	101.0		114.3	90.1	105.4
SEM		10.1	8.6	10.8		16.9	10.6	14.2

No significant differences between tasks for group

b) Subject retested with round coil.

Subject	Preferred hand			
	intensity	Pincer	Power	Rotation
8	T+5	*44	*58	107
	T+8	*62	*58	84

b) Young patients.

Patient	Affected hand				Unaffected hand			
	intensity	Pincer	Power	Rotation	intensity	Pincer	Power	Rotation
AP	T+8	*124	79	77	T+8	*125	100	*127
GJ	T+8	88	80	79	T+7	*64	*63	*136
CS	T+2	53		94	T+6	*180		*138
SO	T+8	*66		176	T+6	105		*141
mean		82.8	79.5	106.5		118.5	81.5	135.5
SEM		15.5	0.4	23.5		24.1	13.1	3.0

c) Old patients.

Patient	Affected hand				Unaffected hand			
	intensity	Pincer	Power	Rotation	intensity	Pincer	Power	Rotation
BH	T+15	81	*51	64	T	85	*51	*296
RB	T+8	*51	*45	*48	T+10	104	*60	102
WH	T+10	94	80	123	T+7	151	127	*269
DF	T+8	98		95	T+1	86		167
mean		81.5	58.7	82.5		106.5	78.0	208.5
SEM		10.6	9.4	19.3		15.5	21.5	45.1

* significantly different from abduction response amplitude.

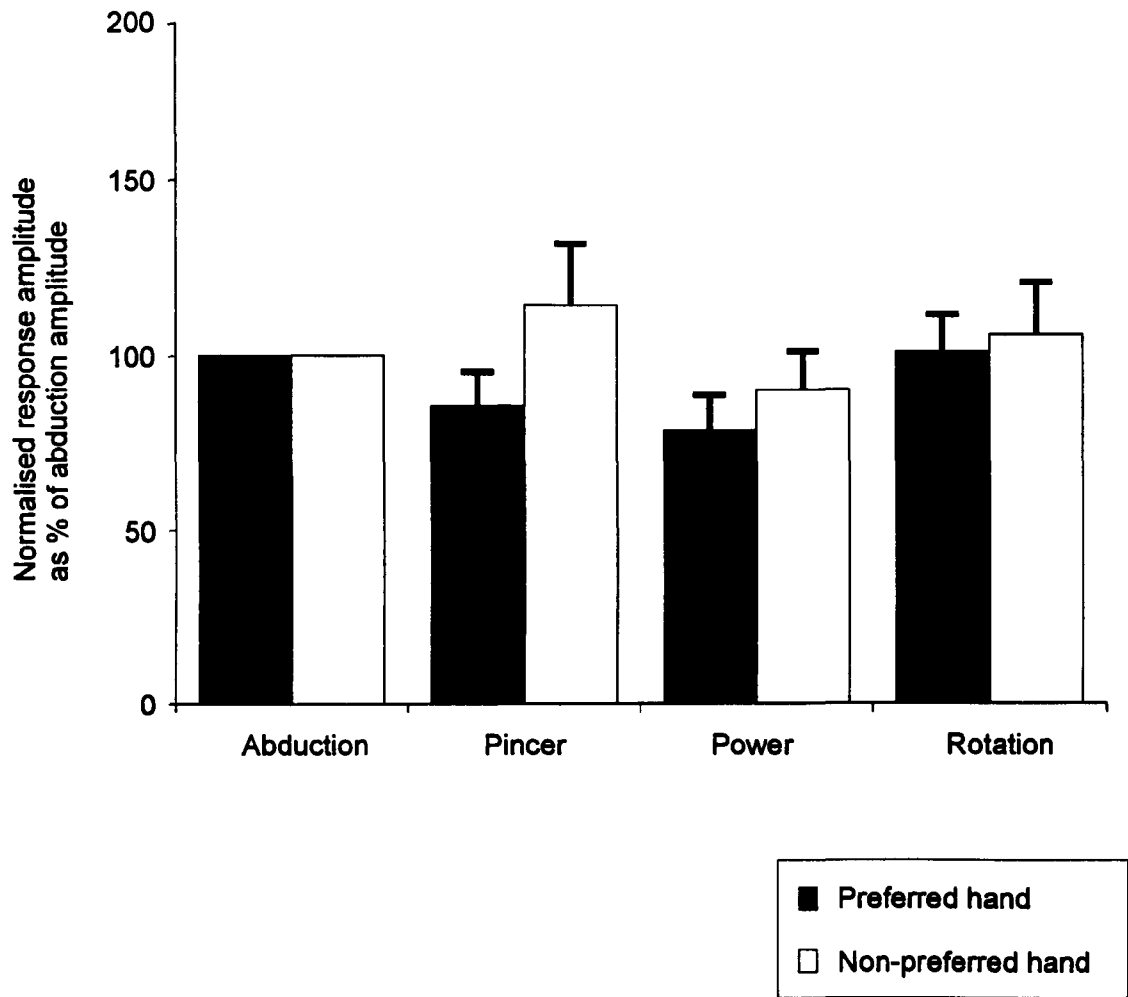


Figure 3.5 Normal older subjects response amplitudes across tasks.

Mean (S.E.M.) 1DI response amplitudes normalised to baseline EMG level for all normal subjects, expressed as a percentage of the response in abduction (100%). There was no significant difference between response amplitudes for complex tasks and abduction for either the preferred or non-preferred hand.

Patients.

Because the results from the normal subjects differed from those of the younger subjects investigated by Flament et al. (1993), it was necessary to compare the patients with normal groups according to age. Therefore the results from patients who were under forty years and over forty years have been displayed separately in table 3.4, c) and d).

As expected, on the unaffected side of the four patients who were under forty years, there were significantly larger responses for at least one complex task compared to abduction. All four patients had large responses during rotation and two of them also had large responses during pincer. However when these patients used the affected hand three of the four had no significantly larger responses for complex tasks. The exception was the best-recovered young patient (AP). She exhibited an essentially 'normal' pattern of responses. During performance of the pincer task, responses were significantly larger than abduction for her affected hand. The results for the young patients are shown graphically in figure. 3.6.

The results from the four older patients, when they used the affected hand, were very like those for the normal age matched group. None of the patients showed larger responses for complex vs. abduction tasks, although two of them had significantly smaller responses. However when using the unaffected hand, two patients had very large responses during rotation. These were substantially larger than any seen in the normal group. In the few normal subjects who had large responses for a complex task, the mean amplitudes were usually less than twice the size of the abduction responses (see table 3.4a). The responses for rotation on the unaffected side of the two patients, were two and a half to three times the size of the abduction responses. The results for the older patients are shown graphically in figure. 3.7.

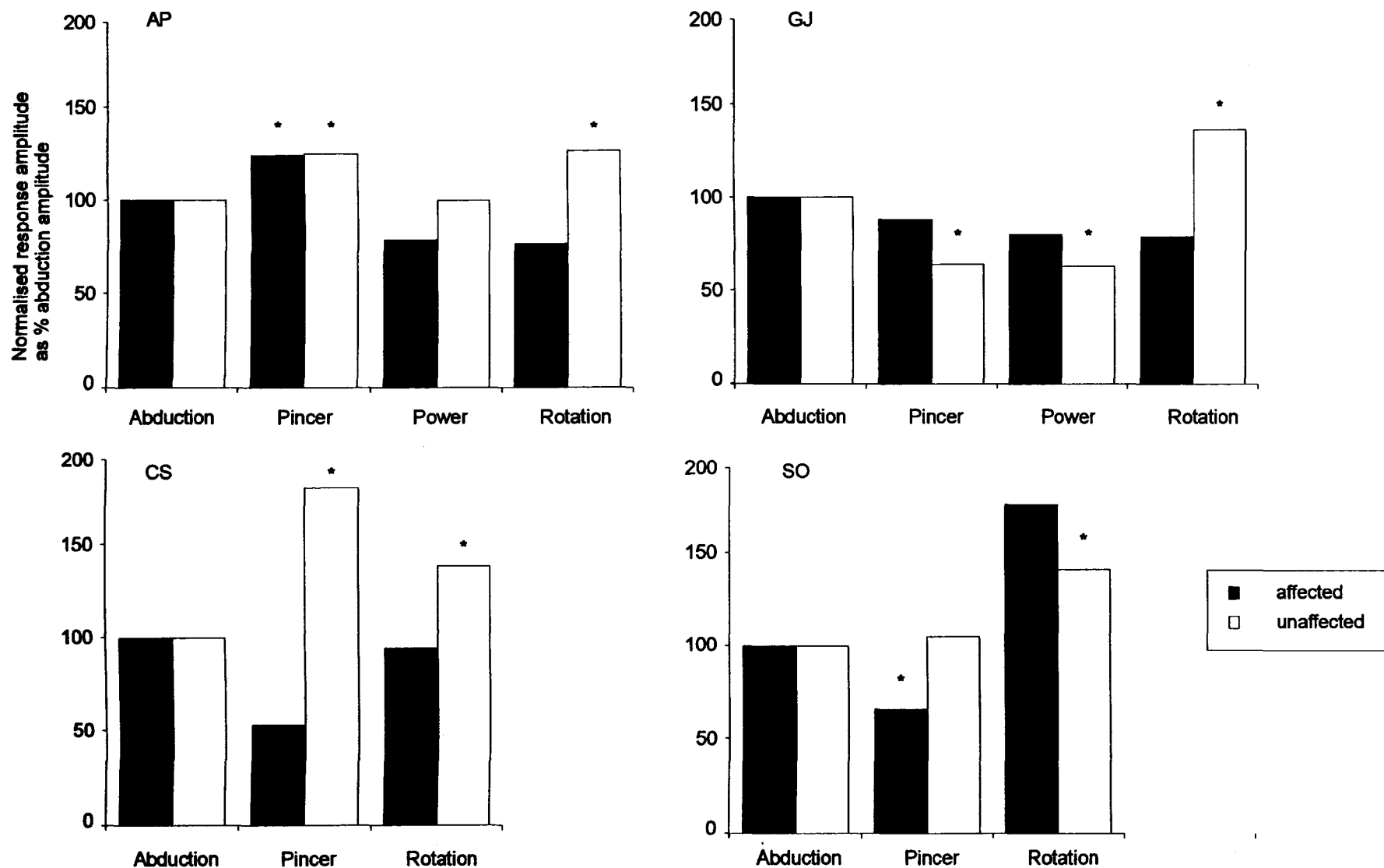


Figure 3.6 Younger patients' response amplitudes across tasks

Mean 1DI response amplitudes normalised to baseline EMG, expressed as a percentage of the response in abduction (100%).

An asterisk denotes statistically significant difference from abduction value (t test).

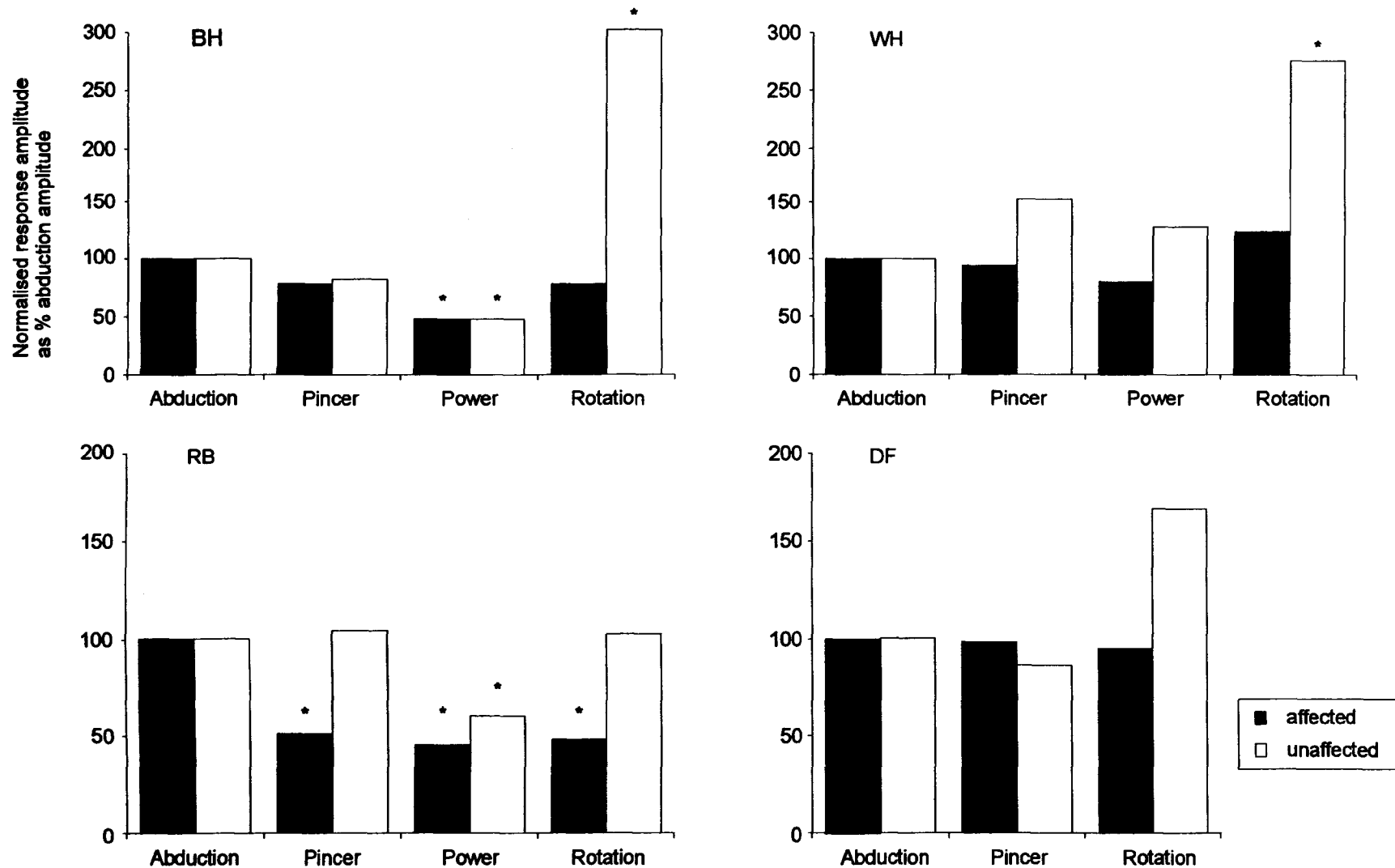


Figure 3.7 Older patients' response amplitudes across tasks.

Mean 1DI response amplitudes normalised to baseline EMG level, expressed as a percentage of the response in abduction (100%). An asterisk denotes statistically significant difference from abduction value (t test). Note different scales for top and bottom charts.

3.4.5 Latency and Duration of responses across tasks.

There was little variation of response latency across tasks in either the normal subjects or the patients' (affected and unaffected hands). Table 3.5 gives the response latencies and durations of responses in the patients. In normal subjects, the variation in latency across tasks was usually less than 1 ms and never more than 2 ms. This was also true for the affected side in the patients. There were two exceptions: two more severely affected patients (SO and WH) shared a variation in response latency across tasks of 6.8 and 2.3 ms, respectively. SO had an extremely long latencies for responses during abduction and pincer tasks, c. 35.5 ms, but during rotation his average response latency was 29 ms.

The range of response duration across tasks was within 6.2 ms in normal subjects and on the unaffected side of the patients. On the affected side, the patients showed a greater variability across tasks than on their unaffected side, but no consistent relationship with response amplitude was apparent.

3.4.6 Ipsilateral responses.

The four patients tested using the small butterfly coil did not have any responses in the 1DI muscle of the affected side when the ipsilateral (undamaged) cortex was stimulated. This was true even for strong stimuli that were clearly supramaximal for responses in the unaffected hand. Stimulation of the damaged side also failed to produce any ipsilateral responses. The three patients tested for ipsilateral responses in the longitudinal study also showed no secure ipsilateral responses in either affected or unaffected 1DI (see chapter 4).

Table 3.5. Patient's response latencies and durations across tasks.

Patient	task	Latency		Duration	
		affected	unaffected	affected	unaffected
WH	abduction	28.5	23.3	8.3	8.3
	pincer	29.3	23.0	15.0	8.0
	power	30.8	23.0	10.0	7.0
	rotation	29.0	22.5	11.0	10.0
	range	2.3	0.8	6.8	3.0
BH	abduction	27.0	24.0	19.0	14.0
	pincer	26.5	23.0	19.0	14.2
	power	25.5	24.0	artifact	14.6
	rotation	26.0	23.0	23.0	14.5
	range	1.5	1.0	4.0	0.6
GJ	abduction	25.0	25.0	24.0	11.3
	pincer	25.3	25.0	20.5	9.3
	power	24.5	25.0	20.5	8.8
	rotation	24.5	24.8	21.0	10.3
	range	0.8	0.3	3.5	2.5
RB	abduction	30.0	27.0	17.0	10.8
	pincer	31.0	27.0	14.3	10.3
	power	30.0	27.0	15.3	10.3
	rotation	31.0	27.0	15.8	15.3
	range	1.0	0.0	2.8	5.0
AP	abduction	19.0	19.5	11.0	8.1
	pincer	19.0	19.5	14.3	11.3
	power	19.0	19.5	11.5	11.1
	rotation	19.0	19.5	10.5	12.0
	range	0.0	0.0	3.8	3.9
CS	abduction	24.8	23.0	22.0	14.3
	pincer	25.5	22.8	12.5	15.4
	rotation	24.8	23.5	22.3	13.8
	range	0.8	0.8	9.8	1.6
SO	abduction	35.8	24.0	8.1	13.0
	pincer	35.5	24.0	14.8	14.0
	rotation	29.0	24.0	10.8	10.5
	range	6.8	0.0	6.6	3.5
DF	abduction	28.3	25.0	28.3	13.3
	pincer	27.8	24.5	28.5	13.5
	rotation	27.3	24.8	31.3	14.8
	range	1.0	0.5	3.0	1.5

3.5 Discussion

3.5.1 Lack of task dependent responses to TMS in older normal subjects.

This study was carried out primarily to see if task dependence of responses is maintained despite the reduction in the size of the CM cell population that is available to the recovered stroke patient. It was therefore somewhat surprising to find that normal subjects who were older than the young adults previously investigated (Flament et al., 1993), did not have larger responses to TMS in 1DI when they were performing complex tasks as compared to simple abduction of the index finger. Pooled results for the group of ten normal subjects aged between 43 and 60 years, showed no significant difference in response amplitudes across tasks. Only two individuals displayed larger responses during rotation or pincer than during abduction. Responses that were smaller than in abduction were in fact more commonly observed. In accordance with previous findings (Schieppati et al., 1996) the onset latency and response durations did not vary according to task.

Previous studies finding clear task-related variation in the size of EMG responses from small hand muscles to TMS have all investigated subjects who were aged between around 20 and 40 years (Datta et al., 1989; Flament et al., 1993; Schieppati et al., 1996). Only one study reported an absence of variation in the size of responses between tasks, but in this case the ages of the subjects were not detailed (Harrison, Mayston and Stephens, 1994). Reasons for the difference between task dependency results for young and old cannot be defined by this study, but there are at least two possible interpretations.

First, there could be an occupational or skill practice explanation. Evidence for greater cortical excitability being related to handedness is sparse, but one TMS study found a relationship between threshold intensity for responses in 1DI and biceps and hand preference for writing (Triggs et al., 1994). In right-handers, the threshold for responses in muscles in the right arm was lower than the threshold for activation of corresponding

muscles in the left arm. In left-handers, the reverse was true. Threshold asymmetry was influenced significantly by the consistency with which each subject used the writing hand to perform other motor tasks, and was not significant between non-consistent left-handers and right-handers. Recently evidence from cortical imaging and mapping techniques has also shown that increased cortical representation of the fingers may be induced by practising an action or by exposure to enhanced sensory stimulation (Pascual-Leone and Torres, 1993; Elbert, Pantev, Wienbruch, Rockstroh and Taub, 1995; Karni, Meyer, Jezzard, Adams et al., 1995; Pascual-Leone, Dang, Cohen, Brasil-Neto et al., 1995). Twelve of the fourteen subjects investigated by Flament et al. (1993) were students, the other two were academics. All of them spent a considerable amount of time writing. Using a pen requires a combination of isometric pincer and rotation actions. These tasks yielded particularly large responses to TMS. Perhaps the results from the younger subjects reflects a change in cortical connections of CM cells and /or their cortical excitability. Interestingly the only two subjects from the older group who showed large responses for pincer or rotation, when using the preferred hand, were also university lecturers, and constant pen users. The other subjects in that group did not engage in a significant amount of writing in their daily activities, although it would still be expected that these older subjects would use the functional grips more frequently in their daily lives than the non-functional abduction task.

Alternatively the lack of clear-cut task variation in older subjects may have been due to the aging process. It has been observed that the amplitude of responses to TMS declines with age (Eisen, Siejka, Schulzer and Calne, 1991). On the basis of early studies that have estimated the number of cells in the cortex (Henderson, Tomlinson and Gibson, 1980) and in spinal cord (Tomlinson and Irving, 1977), this decrease in response amplitudes has been attributed to cortical neuronal loss, more than to attrition in the motoneurone pools (Eisen et al., 1991). However more recent reports have challenged the

classical view that neuronal loss from the cerebral cortex occurs with age (Haug, Kuhl, Mecke, Sass and Wasner, 1984; Terry, DeTeresa and Hanson, 1987). These later cell counts, derived from large samples of adult human brains, and employing techniques that improve the reliability of counting cells using automated imaging equipment, found that rather than a reduction in the total number of neurones, shrinkage of the larger neurones was correlated with aging.

Detailed studies of motor cortex in monkeys have also found no difference in the total number of neurones between young and old monkeys, but degenerative changes were observed in the dendrites situated in the upper layers of the cortex, in cell bodies and in the descending myelinated axons (Tigges, Herndon and Peters, 1990, 1992; Peters, 1993). An interesting finding from examination of layer one of precentral and postcentral cerebral cortex in eleven mature human brains from subjects aged between 45 and 84 years, was that significant decrease in the number of synapses with age was found in the motor cortex but not in the sensory cortex (Adams, 1987). The synapses lost from the motor cortex were from the terminal branches of axons, and from dendritic spines. Accompanying the decline in synapse number was an increase in the mean length of the post-synaptic contact zone of the dendrite shafts. This suggests that the remaining dendrites in layer one increase their length, as if seeking new contacts to compensate for loss of previous inputs, in a manner similar to that found by Darian-Smith and Gilbert (1994) in cat cortex following binocular retinal lesions. Whether it is the quantity of cortical cells, their efficiency, or their connections that are lost with age, the upshot is rather as predicted for the stroke patients: with fewer intact connections in older subjects the different sub-populations of CM cells for different tasks become less and less redundant.

3.5.2 Task-related variation in responses to TMS in stroke patients.

It is likely that the population of surviving CM cells is significantly less after stroke. Responses to TMS in the affected 1DI of most of the patients were of longer latency and duration and had higher thresholds than in the unaffected 1DI. Given that there is good evidence to attribute the short-latency responses seen under normal conditions to repetitive activation of the CST, the late responses in these patients are likely to have resulted from interruption of this pathway within the internal capsule, as confirmed by the CT scans. The longer latency response might indicate a selective loss of the faster-conducting CS neurones, although it is also likely that a much reduced number of CS neurones would result in a slower build up of excitation at spinal levels, resulting in long latency responses. The long response durations may also have been related to the lack of cortical inhibition (Fuhr, Agostino and Hallett, 1991; Schnitzler and Benecke, 1994), perhaps recurrent from CS cells. The higher thresholds for exciting responses may also reflect a smaller number of CS neurones remaining after stroke, and/or a less effective excitation of the damaged side by TMS. A rather unexpected finding was that, in two of the patients (AP and GJ), the threshold was actually lower on the affected side; in both these patients too, latency was similar on both sides. Low thresholds at one year after stroke have been reported previously (Heald et al., 1993a).

The effects of such a reduction in the size of the CM cell population should be examined by comparing the patients with appropriately age matched control subjects. When the patients who were over forty years old performed the isometric grips with the affected hand, the task dependency of the responses was similar to that seen in the age matched normal subjects. None of the responses evoked in the 1DI were larger than when they performed the abduction task. Responses from the two more severely affected patients (WH and DF) completely lacked task-dependent variation, but perhaps these results should be treated with caution since these patients had difficulty controlling the

background level of EMG across tasks. The better recovered patients (BH and RB) had responses in at least one task that were significantly smaller than those evoked during abduction. When the patients used the unaffected hand to perform the tasks, two of them had substantially larger responses for the rotation task. Although responses for the rotation task that were significantly larger than responses for abduction had been present in one or two normal subjects, *none* had been so prominent as the responses in these patients. It is conceivable that over the months that these patients had been unable to use the affected hand, they had become dependent on the unaffected hand and through this increased use there may have been some functional reorganisation within the undamaged cortex. This would argue against the idea that older subjects have too few CM cells or cortico-CM connections to allow task specialisation. It would be interesting to investigate this phenomenon further with a larger group of patients, using TMS and other non-invasive techniques.

The results from the patients who were under forty years were compared with those from the study by Flament et al. (1993). As expected when using the unaffected hand, all four patients had at least one complex task that yielded larger responses to TMS than abduction. When using the affected hand this normal task variation was absent in three of the four patients. Larger responses for complex tasks were only found on the affected side of the best recovered young patient, AP.

I suggest that the most affected patients in the sample, both young and old, were hampered by a much reduced number of effective CM connections to the 1DI muscle; the remaining population may be entirely non-redundant in that patients may try to use the *same* CM cells for performance of each of the different tasks, thereby leading to a loss of the task-related variation in response amplitude. Such a strategy would not be appropriate for producing the specific patterns of muscle contraction the different tasks demanded, and therefore might explain the clumsiness the patients complain of, and which

they exhibited during the hand function tests (see Table 3.1). The slowly recovering patients who were recruited from the longitudinal study were known to have no responses to TMS in the affected 1DI in the early months after stroke. The recovery of their hand function was closely associated with the presence of responses at the six month test and after this time (see chapter 4). This suggests that it is reorganisation of the CST that brings about recovery of hand function and so with further reorganisation there is a potential for the return of task dependent organisation within the damaged cortex of the young patient.

Patient AP might well have reached this stage, her recovery was particularly remarkable. She had complete loss of her arm and hand movement for the first six weeks after stroke, after that her hand function slowly recovered and had reached performance levels that were very close to normal. She used her hand every day at work for counting banknotes. As pointed out above, the threshold and latency of her responses suggest that the original lesion did not cause any *permanent* interruption of the CST. It is possible that reorganisation of surviving CS elements in the well recovered patient once again allows for task-specific recruitment of the remaining CM cells.

3.5.3 Variation in pattern of EMG activity for different tasks is present in stroke patients.

If less skilled patients or indeed some older normal subjects, are recruiting the same population of CM cells regardless of the task then the balance of muscle activity might be identical whenever 1DI was involved in a task, be it index finger abduction, pincer, power or rotation grips. Examination of EMG recordings of 1DI with other muscles ought to show a uniform selection of muscles for the different tasks. However, my recordings showed that although some patients were unable to activate the 1DI in complete isolation for index finger abduction (on either affected or the unaffected side), they did appear to be selecting appropriate muscles for the complex tasks. There were

apparent differences between hands that would explain some of the clumsiness observed in patients' affected hand use. The activity on the affected side was weaker and the pattern of activity less well-defined than on the unaffected side. It is probably the precise balance and timing of muscle activity that is crucial for quick, smooth and accurate hand action (Hoffman and Strick, 1995).

3.5.4 Ipsilateral responses.

Stimulation of either the healthy or the damaged cortex did not produce any ipsilateral responses in the patients. This suggests that ipsilateral pathways were not associated with recovery of hand function. However ipsilateral responses in the hand muscles of recovering stroke patients have been reported previously. Fries et al. (1991) found bilateral responses in thumb muscles when the damaged cortex was stimulated in five patients who had "residual hemiparesis". Fries et al. also observed that when their patients attempted to move the paretic hand, the unaffected hand appeared to copy or mirror the movements. Mirroring of EMG was seen in some of the patient's EMG recordings, but mirroring and ipsilateral responses are often dissociated and depend on the age of the patient when the lesion occurred (Carr et al., 1993).

All but one of the patients investigated in this study were seen late after stroke (6 months to 10 years), when much of the patients' recovery is expected to have already been accomplished (Wade, Langton Hewer, Wood, Skilbeck and Ismail, 1983). It is possible that ipsilateral responses are a transient phenomenon seen shortly after stroke. This issue is addressed further in the longitudinal study of recovering patients (see chapter 4).

3.5.5 Conclusion

This study has allowed us to gain some insights into the effects of reduction in the size of the CM cell population on task-related organisation of the CS system after stroke and has shown that responses to TMS in older normal subjects do not show the same clear cut task dependency as has previously been found in young subjects. Further inquiry is needed to establish whether practice or age are important. If practice influences reorganisation of the CS pathway then my findings suggest that patients should be encouraged to practice various hand actions rather than isolated movements and practise them rigorously.

CHAPTER FOUR.

CONTRALATERAL AND IPSILATERAL EMG RESPONSES TO TRANSCRANIAL MAGNETIC STIMULATION DURING RECOVERY OF ARM AND HAND FUNCTION AFTER STROKE.

4.1 Summary

The relationship between the recovery of hand and arm function in a group of hemiplegic stroke patients and the presence of short-latency EMG responses to TMS in four different upper limb muscles (deltoid, biceps, extensor digitorum communis (EDC) and the 1DI) was examined. Twenty one patients were examined within five weeks of stroke (median two weeks), and then at regular intervals over the next 12 months.

Some patients recovered rapidly (Group A); in others recovery was slow and incomplete (Group B). Even at the first test, Group A patients had responses to TMS in all muscles. Most Group B patients initially lacked responses in all tested upper limb muscles; in those that later were able to activate hand muscles, responses returned at or just before this stage of recovery. No such clear correlation between the presence of responses to TMS and ability to activate more proximal arm muscles was evident. Response latency was initially long and declined in a manner that was highly correlated with muscle strength and hand function test scores.

Ipsilateral responses were elicited from both the affected and unaffected hemispheres. Ipsilateral responses from the latter were most common in the proximal muscles of the affected limb, and had latencies that were longer than those elicited in the contralateral (unaffected) arm. Nine cases of ipsilateral responses in hand muscles were found; such responses are not found in healthy subjects. Ipsilateral responses from the undamaged hemisphere were more prevalent in the poorly recovered patients: the mechanisms that underlie may not be beneficial for recovery.

4.2 Introduction

Capsular lesions or infarcts in the cortical motor areas have different effects on the strength and usage of different upper limb muscle groups (Walshe 1947; Colebatch and Gandevia 1989). Usually it is the more distal hand and finger muscles which are most profoundly affected, with less involvement of the more proximal muscles. These effects are consistent with the pattern of excitatory CS influence on different upper limb motoneurons (Palmer and Ashby 1992; Schoen 1964; Nathan and Smith 1955; Clough, Kernell and Phillips, 1968; Kuypers 1981; Porter and Lemon 1993, pp 83-88). Further, if recovery from stroke occurs, it is usually the case that strength and movement return at the shoulder and elbow earlier than in the hand, and fine finger movements often remain permanently disrupted (Twitchell 1951).

The mechanisms that influence recovery are still largely unknown and unexploited for the benefit of the patient. They may involve CS fibres derived from non-primary motor cortical areas (Weiller et al. 1993; Fries et al. 1993). A further contribution may come from the intact hemisphere (Fisher 1992; Chollet et al. 1991), and could involve ipsilateral CS fibres (Wasserman et al. 1991, 1994; Carr et al. 1994).

This chapter describes the use of TMS to investigate the reorganisation of the descending motor pathways associated with recovery of upper limb function after stroke. Responses to TMS in the most severely affected hemiplegic patients are usually absent (Berardelli et al. 1987; Thompson et al. 1987; for a review, see Escudero et al. 1992). In less affected patients responses are of longer latency, smaller amplitude and have higher thresholds than on the "unaffected" side (Abbruzzese et al., 1991; Hömberg et al. 1991; Escudero et al. 1992; Ferbert, Vielhaber et al. 1992; Heald et al. 1993a,b). The presence of EMG responses to TMS have been found to correlate with functional recovery after stroke (Hömberg et al. 1991; Ferbert, Vielhaber et al. 1992; Heald et al. 1993b) and responses reappear when patients regain voluntary contraction of a given muscle (Heald

et al. 1993a,b; Escudero et al. 1992). However, it is not known to what extent this is due to the recovery of CS influence. The absence of an EMG response in a paralysed muscle cannot be taken as evidence that TMS is failing to excite a CS volley (Heald et al. 1993b). The return of voluntary activation could reflect the recovery of other, non-corticospinal excitatory inputs to the motoneurone pool; the raised excitability at spinal levels provided by these inputs might then be sufficient to allow CS volleys excited by TMS to produce EMG responses.

This investigation represents a longitudinal study of a small but carefully selected cohort of hemiplegic patients, which had the following objectives: first, because of the different effects of stroke on different muscle groups, a detailed comparison of responses from intrinsic and extrinsic hand muscles, as well as for muscles acting at the elbow and shoulder was made. The accessibility of the motoneurone pool to TMS with the degree of voluntary activation of the same motoneurone pool at different times after stroke was compared, in the hope that this would reveal further insights into the importance of the CS system for voluntary activation of different muscles. Second, I wished to look for correlations between these observations and the recovery of hand function, assessed with a battery of tests. Third, special attention was paid to the existence of responses excited by TMS in *ipsilateral* muscles, because of the possible contribution of the undamaged hemisphere to recovery of function.

4.3 Methods

4.3.1 Patients.

Twenty one patients participated in this study (11 males; 10 females). They were aged from 22 to 77 years. TMS was carried out for the first time between 3 days and 5 weeks after stroke (median 2.0 weeks); patients were tested at regular intervals thereafter (typically at 6 weeks and at 3, 6 and 12 months after stroke). The day after each TMS

investigation the patient's upper limb motor function was assessed (see chapter 2, section 2.2).

4.3.2. EMG recording

Surface EMGs were recorded from 1DI, EDC, biceps brachii and middle deltoid on both sides. The test manoeuvres for activating these muscles were: holding both upper arms in abduction (deltoid), flexing the supinated forearms (biceps), extending all metacarpophalangeal and interphalangeal joints (EDC) and abducting the index fingers on both sides (1DI).

4.3.3 Experimental Procedure

The EMG activity produced during MVC of each muscle was recorded. With the coil positioned over the intact hemisphere, in the optimum position for a short latency EMG response from the gently contracted 1DI on the contralateral side (see chapter 2, section 2.6), the patient was then asked to relax and the threshold for responses in each test muscle on the unaffected side was determined in the relaxed state.

The stimulator was then set to deliver stimuli at the maximum comfortable intensity: 70% max. output (Digitimer) and 55% (Magstim). Threshold tests on normal subjects showed that these intensities are approximately equivalent. These intensities were both well above the normal threshold intensities needed to obtain responses from distal upper limb muscles. They were also high enough to obtain responses from proximal muscles in normal subjects when a little voluntary background contraction was applied, but not always when the muscle was at rest.

The patient was asked to attempt to make bilateral contractions, in turn, of the four pairs of muscles, while 10 stimuli were delivered. Whenever possible, visual feedback of EMG activity from the muscle contralateral to the cortex being stimulated was provided in the form of a vertical array of lights. The patient kept activity at about 10% of MVC, and was asked to match the effort, if possible, from the homologous muscle on the other

side.

The procedure was then repeated for the affected side. Coil position over the damaged hemisphere was determined in the same way as for the unaffected side. In cases where no responses could be obtained from the affected side, the coil was positioned at the mirror image of the point on the unaffected hemisphere. When the patient was unable to generate any activity in the affected muscle he or she was encouraged to try to do the action even though no contraction was evident. In some patients, percutaneous electrical stimulation of the ulnar nerve at the elbow was applied to obtain M waves from the 1DI. This allowed a comparison to be made between the amplitude of the M wave and that of the responses evoked by TMS.

4.4.4 Categorization of responses to TMS

EMG averages were categorized according to the presence of a response to TMS and the patient's ability to voluntarily contract the muscle (figure 4.1). The categories were:

1. No response to TMS, no voluntary EMG activity.
2. Response to TMS, no voluntary EMG activity.
3. No response to TMS, voluntary EMG activity.
4. Response to TMS and voluntary EMG activity.

In a given muscle, voluntary EMG activity was always clearly present when the MVC for that muscle was equal to or exceeded MRC grade 2 (i.e. able to move but unable to hold against gravity).

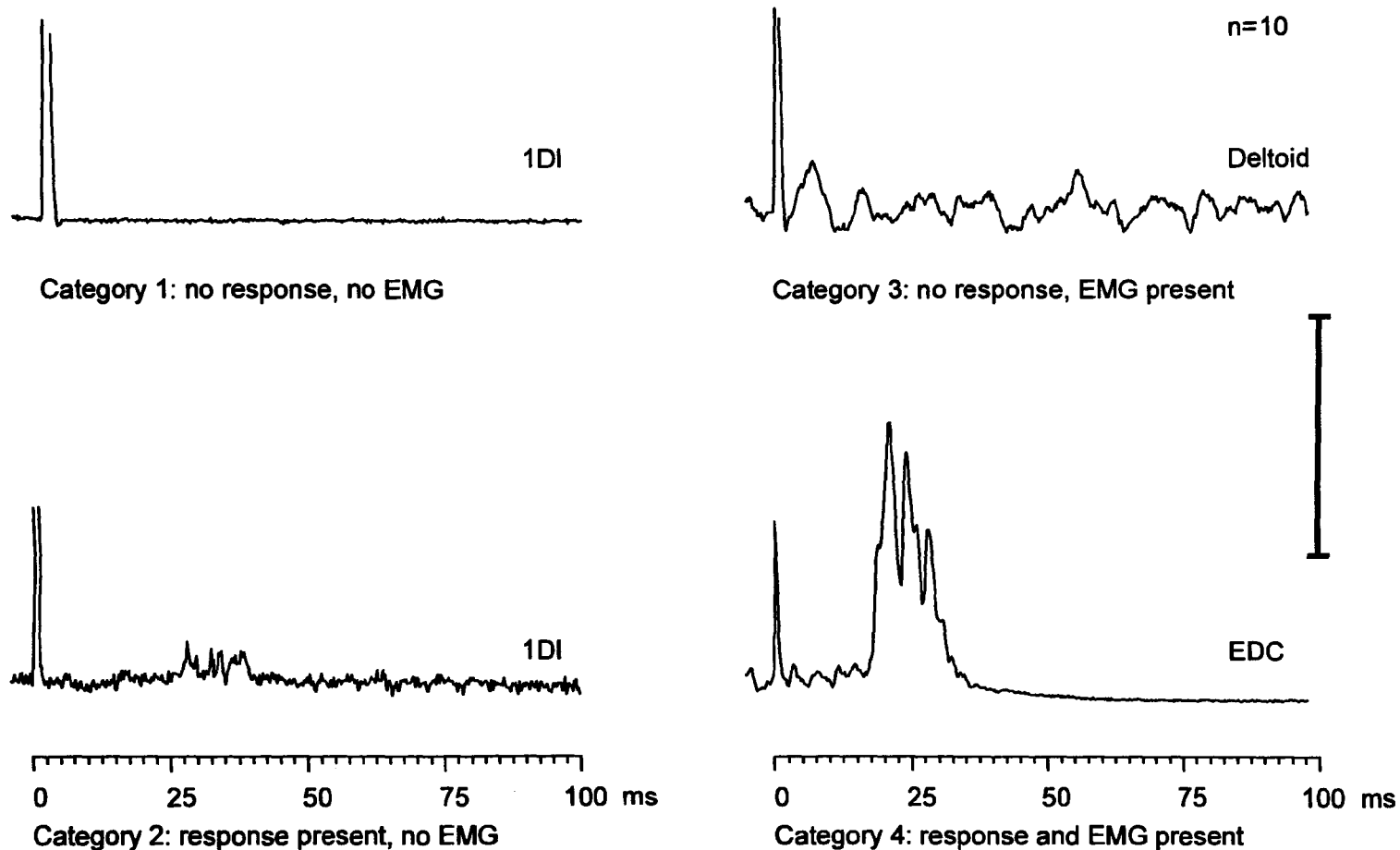


Figure 4.1 Response categories.

The four categories of EMG response to TMS in stroke patients following stimulation of the damaged cortex at 70% max. stimulator output (Digitimer stimulator). Each trace is a rectified average of 10 sweeps. In each case the patient was attempting to contract the muscle being tested. Successful voluntary activation was defined as being equal to or exceeding MRC grade 2. At this level of contraction EMG activity was easily detectable. The calibration bar represents 100 microvolts for the illustrations of categories 1, 2 and 3 and 500 microvolts for category 4.

4.4 Results

4.4.1 Recovery of motor function in hemiplegic patients

Eighteen patients were tested up to twelve months after stroke. The remaining three were followed for six months. Table 4.1 gives the patients' details, including the lesion site assessed from CT scan reports. Most patients were scanned within the first two days after onset of stroke. Patients were divided into two groups, A and B, according to whether they were able (Group A, n=8) or unable (Group B; n=13) to perform the peg test at six weeks after stroke.

All but one of the Group A patients had some degree of arm movement at the time of admission to hospital. At the time of their first TMS test they were all scoring over 45 points on the motricity index, and had no apparent sensory deficits (cutaneous or proprioceptive). Their recovery was rapid and, by six months, four of the six were scoring 100 points. All of them reported that they were using the affected hand for everyday activities such as using a knife or fork, gripping and carrying everyday objects. Four were able to perform the peg transfer task within the normal time limits.

The more severely affected Group B patients generally had larger lesions than the patients in Group A and often had sensory, perceptual, cognitive or language deficits in addition to their weakness. They recovered more slowly and had poorer functional outcome, as expected from the clinical literature (Allen 1984; Bamford, Sandercock, Dennis, Burn and Warlow, 1991). On admission they had no detectable arm movement and by the time of their first test few had more than a flicker of activity in any of the muscles tested. At six months all but three (FD, SO and RD) were still well below the maximum motricity score, and were unable to use the affected limb in the course of daily living. FD and SO were able to do the peg test by this time, but were slower than normal for their ages, and by the end of the one year follow-up period, two others: DF and RD, were also able to complete the test.

Table 4.1 Patients details.**Group A Patients.**

Patient	Sex	Age	Weak Arm	Sensory, perceptual or cognitive impairments, additional to weakness, on entry to the study	Lesion site identified on CT scan, (cortical or sub-cortical)	Motricity index upper limb score (max=100 points)	
						At first test (wpo)	At 6 months
FC	m	74	L	none	Sub-cortical: small infarct R internal capsule	66 (5)	77
GR	f	70	R	none	Cortical and sub-cortical: L fronto-temporal region	61 (3)	85
WS	m	52	R	dysphasia.	None identified	93 (1)	100
AG	m	77	L	poor coordination	None identified	84 (3)	100
CS	m	22	R	none	Sub-cortical: small infarct L internal capsule	46 (0.5)	100
AM	f	44	L	poor coordination	Cortical: R small infarct	100 (2)	100
SK	f	72	R	none	No scan	62 (2)	92
PP	f	63	L		Subcortical: R small infarct	66 (1)	84
Median		66.5				66	96

Group B patients

DF	m	68	R	none	Sub-cortical: small infarct L internal capsule	1 (2)	61
JB	m	57	R	dysphasia. Sensory/proprioceptive loss.	Cortical and sub-cortical: large L haemorrhage	1 (5)	29*
JR	f	67	L	inattention to left. unable to test sensation/proprioception.	Cortical and sub-cortical: R frontal lobe infarct	10 (2)	29
SC	m	72	R	dysphagia, sensory loss.	Subcortical: Haematoma L internal capsule	10 (0.5)	59
SR	m	70	L	homonomous hemianopia, L inattention, Sensory/proprioceptive loss.	Cortical and sub-cortical: large R cerebral infarct	1 (2)	1
DH	f	76	L	L inattention	Cortical and sub-cortical: large R cerebral infarct	10 (3)	29*
KC	f	54	R	expressive aphasia, apraxia, Sensory/proprioceptive loss.	Cortical and sub-cortical: large L cerebral infarct	1 (1)	59**
PW	f	66	L	impaired sensation visual-spatial and cognitive deficits.	Subcortical: R internal capsule infarct	29 (4)	67
SO	m	37	R	none	Subcortical: small haemorrhage L internal capsule	1 (1)	73
RD	f	52	R	expressive dysphasia.	Subcortical: small L internal capsule infarct.	10 (1)	73
ES	m	48	L	Sensory/proprioceptive loss, left inattention, visuospatial and cognitive deficits.	Cortical and subcortical: large R cerebral infarct	1 (1)	19*
GD	f	72	R	none	Cortical and subcortical small L cerebral infarct	19 (1)	56
FD	m	52	R	Sensory impairment in hand.	Subcortical: small L external capsule infarct	62 (4)	85
Median		66				10	59

Note:

wpo = weeks after onset of stroke

* recovered only proximal movement in synergy, ** recovered only proximal movement but out of synergy.

4.4.2 Motor recovery and category of contralateral responses from the affected side.

From the time of the first investigation, all but two of the Group A patients could generate voluntary activity in all muscles and had responses in all muscles to TMS when it was delivered to the damaged hemisphere during active contraction of the muscle. The exceptions (CS and SK) were unable to generate any more than a flicker of activity (MRC grade 1) in 1DI and EDC. However late responses to TMS were obtained in these patients at this first test, and by the time of their next tests, at two and six weeks respectively, both patients were able to generate voluntary activity and movement in these distal muscles.

In contrast, eleven out of the thirteen Group B patients were unable to generate voluntary activity (MRC grade 2 or more) in the affected muscles when first seen, and in eight of these patients no responses were obtained to TMS delivered to the damaged hemisphere. Three patients were unable to generate any activity but had responses in at least one muscle at the first test (SO, RD and GD). These three all recovered some activity in that muscle by the time of the next test four weeks later. Two patients (PW and FD) had both voluntary activity and responses to TMS.

There were clear changes in response category with recovery after stroke. In all those Group B patients who regained the ability to activate distal muscles, responses to TMS accompanied or preceded the recovery of voluntary contraction. Thus no category 3 responses were seen in distal muscles: if the patient could activate EDC and 1DI, responses to TMS were always present (see figure 4.4).

This was not true for proximal muscles, where the return of voluntary activity in deltoid and biceps was not always accompanied by a response to TMS (category 3: see figure 4.4). The appearance of responses was not dependent on the patient's ability to move out of the flexor synergy. Thus for the proximal muscles, my results suggested a

dissociation of the pattern of TMS response from the voluntary activation, which was in distinct contrast to the case for 1DI and EDC muscles.

Response categories from 1DI, EDC and deltoid, and motor recovery are plotted as a function of time after stroke in figure 4.2. Results from two contrasting Group B patients, DF and JB are shown together with values for Group A patients.

The changes in response amplitude and latency with recovery in a single patient are also illustrated in figure 4.3. Response latencies decreased and amplitude increased as the MRC scores improved. For 1DI the ratio of the peak amplitude of the TMS response to that of the M wave elicited from the ulnar nerve, steadily increased during recovery. Expressed as a percentage of the corresponding ratio of the unaffected side it increased from 3.5% (7 weeks), to 13% (13 weeks) and 29% (24 weeks) in this patient.

Figure 4.4 plots the proportion in each of the four categories of all the results obtained from all patients over the entire period of the study. Category three responses (voluntary EMG, but no response to TMS) were found in proximal but not in distal muscles. Category one responses (no response, no EMG) were more common in 1DI and EDC, confirming that, in these patients, the more distal muscles were more affected than proximal.

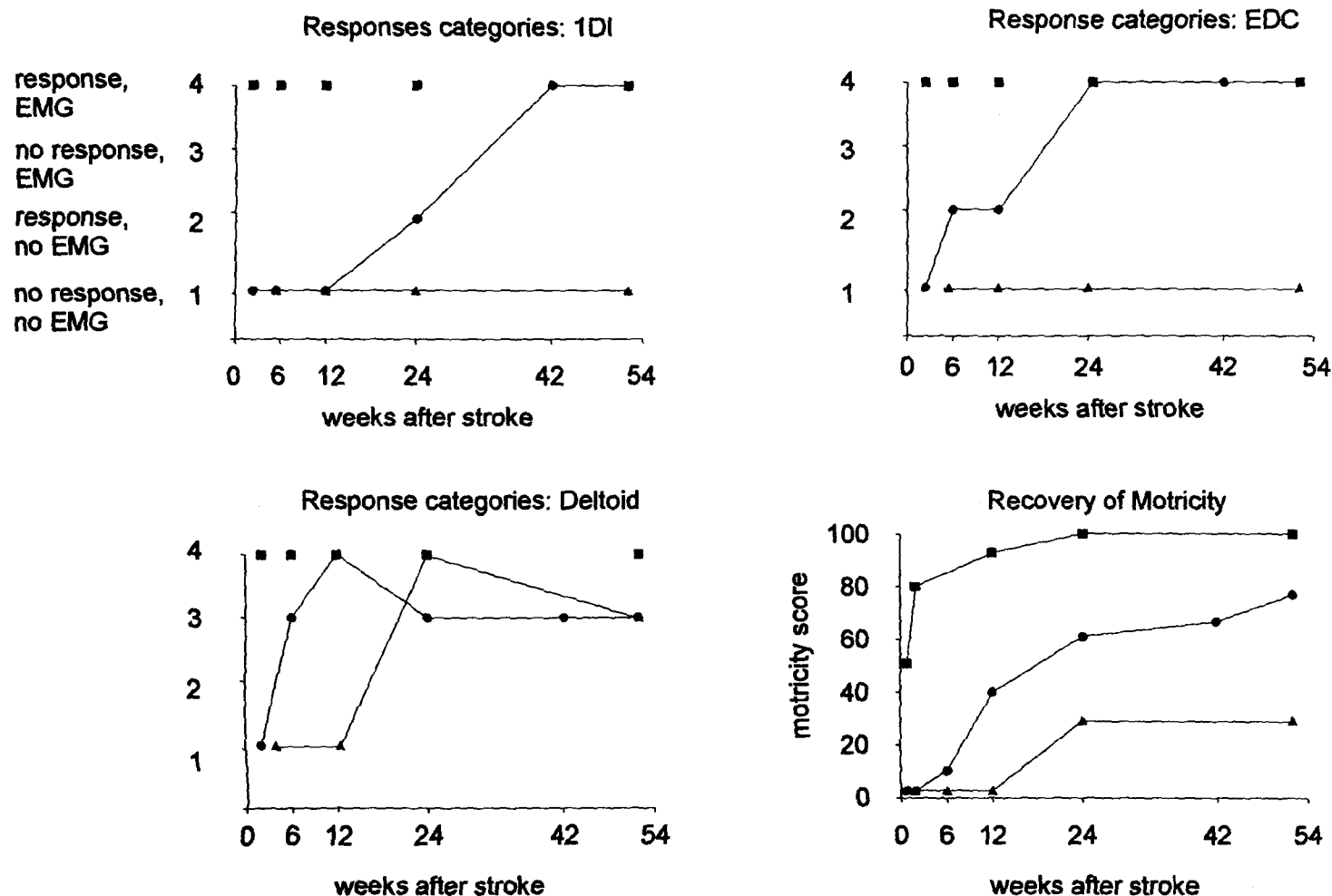


Figure 4.2 Response categories and motor recovery with time after stroke.

Changes in category of response evoked from 1DI, EDC and deltoid in the weeks following stroke plotted for two Group B patients with slow recovery (DF and JB) and for Group A patients, with rapid recovery. All group A patients but one had category 4 responses in all muscles from the earliest test. The motricity scores for DF and JB are plotted lower right, together with the median motricity scores for all Group A patients.

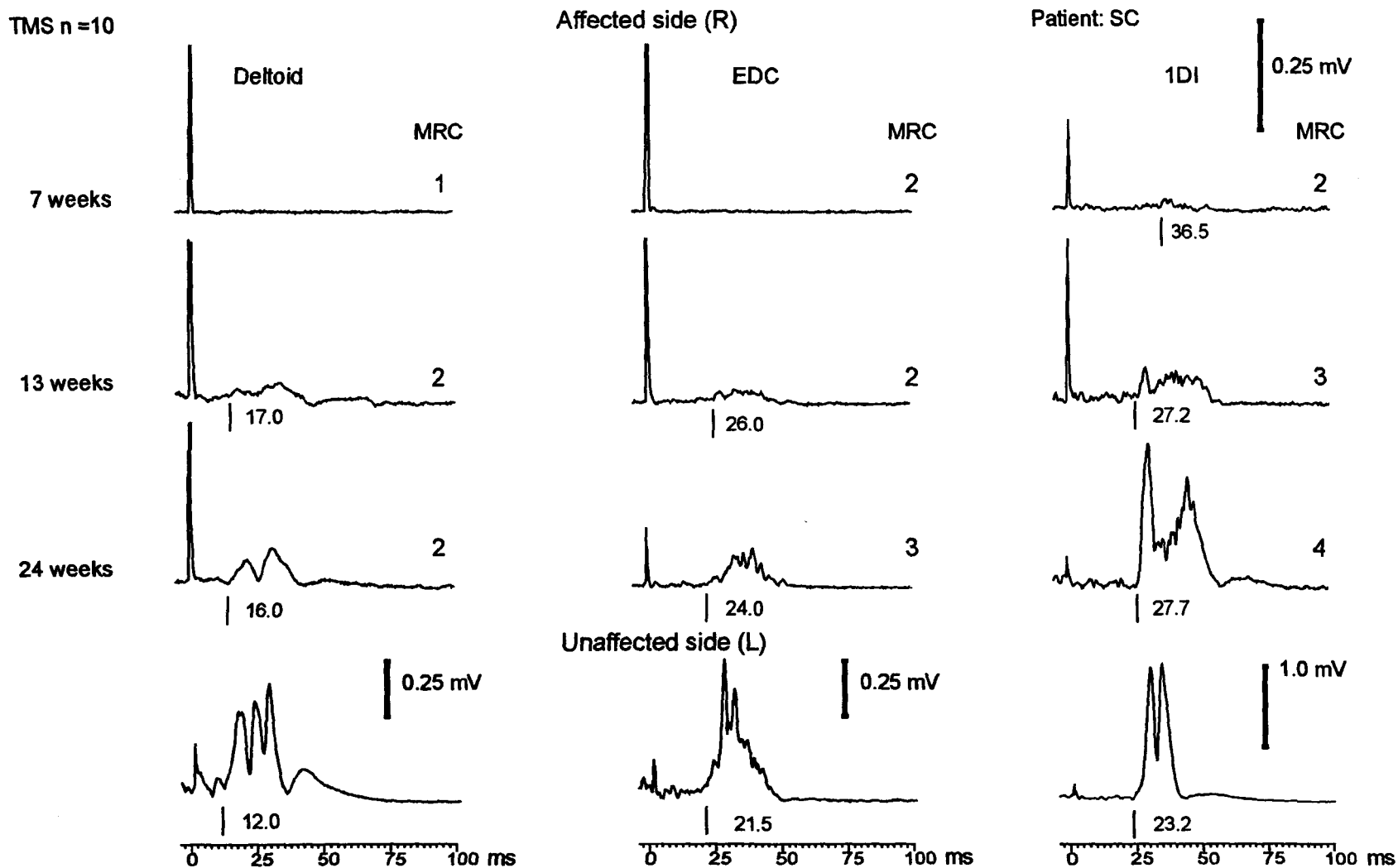


Figure 4.3 Changes in responses to TMS with recovery.

Averaged responses of rectified EMG ($n=10$) in 1DI, EDC and deltoid on the affected side from a single Group B patient, at 7, 13 and 24 weeks after stroke. The MRC grade attributed to each muscle at the time of testing is shown above each trace. Note recovery of responses and shortening of latencies. At 7 weeks there was no response and no EMG on the EDC record; however, during the clinical assessment on the day after the TMS the patient could occasionally produce an MRC grade 2 contraction, but he was unable to maintain it for more than a second. Responses from the unaffected side at 24 weeks are shown in the bottom row of traces. The calibration bar at top right applies to all muscles on the affected side.

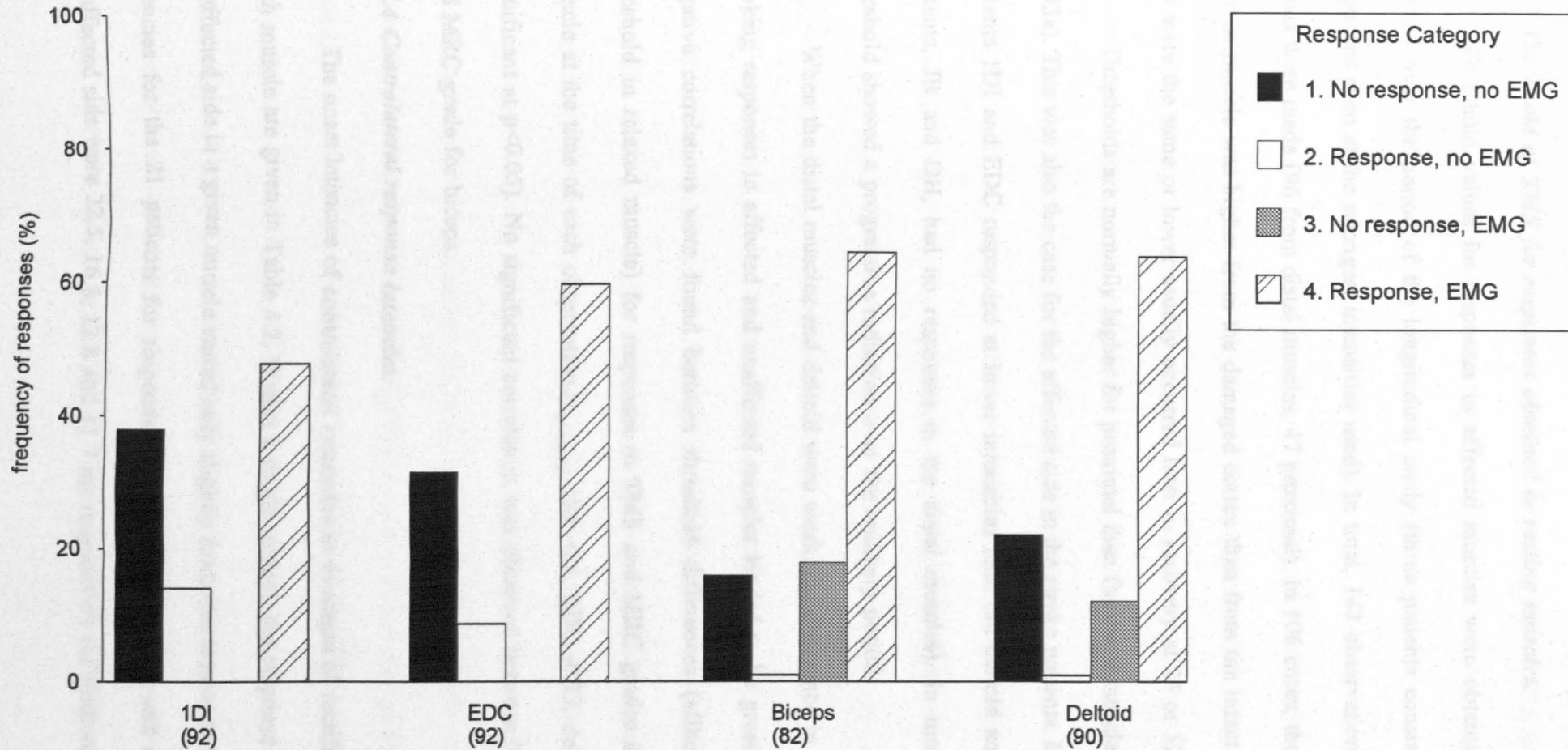


Figure 4.4 Distribution of responses by category.

The results of all recordings by patients over the entire study have been plotted according to the category into which they fell. Numbers of observations for each muscle are given in brackets.

4.4.3 Threshold of TMS for responses obtained in resting muscles.

Threshold values for responses in affected muscles were obtained in eighteen patients over the period of the longitudinal study (three patients consistently had no responses even at the strongest intensities used). In total, 143 observations of threshold values were made (96 from distal muscles, 47 proximal). In 106 cases, the threshold for a given muscle was higher from the damaged cortex than from the intact cortex. Those that were the same or lower usually occurred later in recovery at 24 or 52 weeks.

Thresholds are normally higher for proximal than for distal muscles (Heald et al. 1993a). This was also the case for the affected side in the stroke patients. In 16 out of 18 patients 1DI and EDC responded at lower intensities than did deltoid and biceps (two patients, JB and DH, had no responses in the distal muscles). In nine patients the threshold showed a progressive reduction over the recovery period.

When the distal muscles and deltoid were weak, the difference in thresholds for evoking responses in affected and unaffected muscles tended to be greater. Significant negative correlations were found between threshold differences (affected-unaffected threshold in relaxed muscle) for responses to TMS and MRC grades in the affected muscle at the time of each observation. (r_{spearman} : 1DI -0.4, EDC -0.37, deltoid -0.51, all significant at $p < 0.05$). No significant correlation was observed between TMS threshold and MRC grade for biceps.

4.4.4 Contralateral response latencies.

The onset latencies of contralateral responses in averages of rectified EMG from each muscle are given in Table 4.2. Within a single subject, the response latency on the unaffected side in a given muscle varied only slightly from one session to the next. Mean latencies for the 21 patients for responses in 1DI, EDC, biceps and deltoid on the unaffected side were 22.5, 16.8, 12.8 and 11.7 ms respectively (cf Rothwell et al. 1991).

Standard deviations were close to 2 ms for all muscles on the unaffected side. The coefficients of variation ranged from 8.2% to 15.8%. It is noteworthy that absolute latencies were thus no more variable than estimates of central motor conduction time (CMCT) published previously (Heald et al. 1993a; see Rothwell et al. 1991).

For the tests in which responses to TMS were obtained for the first time, 17 patients had response latencies on the affected side that were greater by at least 2 S.D. of the unaffected side for at least one muscle. In 15 of these patients the affected side latencies were at least 2 S.D. longer than the group mean latencies for unaffected muscles shown in Table 4.2. Two patients had normal response latencies: AM, even at the earliest test, and JB, when responses were first obtained in biceps and deltoid at 24 weeks.

Of the 17 patients who had longer latencies early in recovery, 11 patients subsequently demonstrated shorter latencies in at least one muscle, and these latencies approached the value on the unaffected side.

4.4.5 Contralateral Response latency and Motor Function

The contralateral response latency was analyzed in relation to the ability to contract the muscle and to peg test performance. I first calculated the difference in response latency between the affected and unaffected side, and then ranked them into one of four classes: 'normal' (latency difference ≤ 3 ms); 'long' (> 3 ms and ≤ 10 ms); 'abnormally long' (> 10 ms) and no response'. Spearman rank correlations were made for all Group A and B patients (see table 4.2). There was a significant ($s; p < 0.05$) correlation between latency category and MRC grade for the both distal and proximal muscles. The longer latencies in weak muscles may in part reflect the difficulty some patients had in maintaining a background level of activation, since it is well known that responses from resting muscles are of longer latency than from active muscles (Hess et al. 1987; Thompson et al. 1991; Heald et al. 1993b).

Peg test performance in Group A patients and Group B patients who could do the test was significantly correlated with response latencies in 1DI and biceps, but not EDC and deltoid (table 4.2). This was demonstrated by correlating the ratio (affected/unaffected time score) with the absolute differences in response latency between affected-unaffected side.

4.4.6 Ipsilateral Responses

Ipsilateral responses were observed in some, but not all patients. They were obtained from both proximal and distal muscles, and from stimulation of intact and damaged hemispheres. Altogether 51 ipsilateral responses were obtained from the intact hemisphere and 67 from the damaged cortex in 690 tests. Table 4.3 gives the total number of ipsilateral responses observed from each muscle obtained from all sessions. All ipsilateral responses were recorded while the patient was attempting to make a bilateral contraction, but about one third of responses were seen in muscles that were not the focus of the contraction task. Ten responses were observed in muscles when there was absolutely no background EMG activity present.

When the junction of the double cone coil was centred over the hand region of one hemisphere, part of the coil lay over the contralateral hemisphere. It was therefore possible that some of the ipsilateral responses may have resulted from activation of the contralateral cortex by the outermost rim of the coil (see figures 4.5 a and b). To control for this, *only those ipsilateral responses obtained with stimulus intensities that were as low, or less than the threshold for a response from the resting muscle when it was activated from the contralateral hemisphere, were included in the analysis.* Table 4.3 gives an analysis of these "secure" ipsilateral responses.

Forty five responses resulted from stimulation of the intact hemisphere in 273 tests, and 15 responses were recorded from 80 tests of the damaged hemisphere. Since higher

intensities were needed to obtain responses in the affected arm when the damaged hemisphere was stimulated, many more *tests* examining ipsilateral responses in the affected limb from the intact hemisphere are included in the "secure" count. Thirty six of the ipsilateral responses from stimulation of the intact hemisphere were in proximal muscles. Thirty nine of the 45 ipsilateral responses evoked by stimulation of the intact hemisphere were in Group B patients (i.e. those with poorer motor recovery), and 15 of these responses came from patients who had no responses in the same muscles when the damaged hemisphere was stimulated. Figure 4.6 is an example from patient JB. He had no response in the right affected 1DI from stimulation of the damaged left cortex, but a small response produced when the intact right cortex was stimulated.

Ipsilateral responses from the damaged cortex that were considered to be secure were also more common in Group B patients (10/15 responses).

4.4.7 Latencies of Ipsilateral Responses.

Ipsilateral responses in EDC, biceps and deltoid from stimulation of the intact cortex had latencies that were longer than normal (i.e. longer by at least 2 S.D. than the contralateral response latencies on the unaffected side). In contrast three of the five ipsilateral responses in the affected 1DI had latencies that were within 2 S.D. of the normal times. Ipsilateral responses from stimulation of the damaged hemisphere had short latencies in 1DI and EDC, but most proximal muscle responses had significantly longer latencies.

4.4.8 Time course of ipsilateral responses after stroke.

There was no consistent pattern in the appearance of ipsilateral responses with time after stroke. Ipsilateral responses were recorded in early and late test sessions. Secure responses were obtained from the same muscles on more than one occasion in eight patients.

Table 4.2**Contralateral response latencies on unaffected (unaff) and affected (aff) sides.**

	1DI		EDC		Biceps		Deltoid	
	unaff.	aff.	unaff.	aff.	unaff.	aff.	unaff.	aff.
no. of observations	91	55	89	59	78	52	87	58
no. of patients	21	16	21	16	20	18	21	18
mean (ms)	22.5	26.7	16.8	22.0	12.8	18.9	11.7	15.6
SD	1.8	4.2	1.8	4.7	2.0	7.0	1.8	4.8
SD/mean (%)	8.2	15.9	10.8	21.7	15.8	37.1	15.0	30.7
shortest	18.8	21.0	14.0	16.0	9.5	10.0	9.0	9.8
longest	27.3	40.3	21.8	33.5	16.3	37.8	16.8	36.8

Correlations:

latency categories x MRC grades.	0.82*	0.77*	0.57*	0.62*
(no. of observations)	(90)	(89)	(78)	(87)
latency difference x peg test time	0.62*	0.21	0.72*	0.21
(no. of observations)	(36)	(36)	(29)	(32)

* significant, $p < 0.05$.**Table 4.3 Ipsilateral responses from intact and damaged hemispheres.**

	Intact hemisphere				Damaged hemisphere			
	1DI	EDC	Biceps	Deltoid	1DI	EDC	Biceps	Deltoid
total responses	7	7	24	13	16	17	15	19
(no. of tests)	(89)	(89)	(78)	(89)	(89)	(89)	(78)	(89)

Secure responses: i.e. test intensity \leq to contralateral passive threshold .
(number of tests)

group A	0 (11)	0 (8)	3 (19)	3 (26)	2 (6)	2 (4)	1 (9)	0 (11)
group B	5 (49)	4 (49)	20 (52)	10 (59)	1 (2)	2 (3)	3 (19)	4 (26)
latency range								
shortest	20.0	23.5	17.7	15.7	20.5	15.5	13.7	14.7
longest (ms)	32.7	35.5	40.5	41.2	23.0	23.7	22.7	19.0

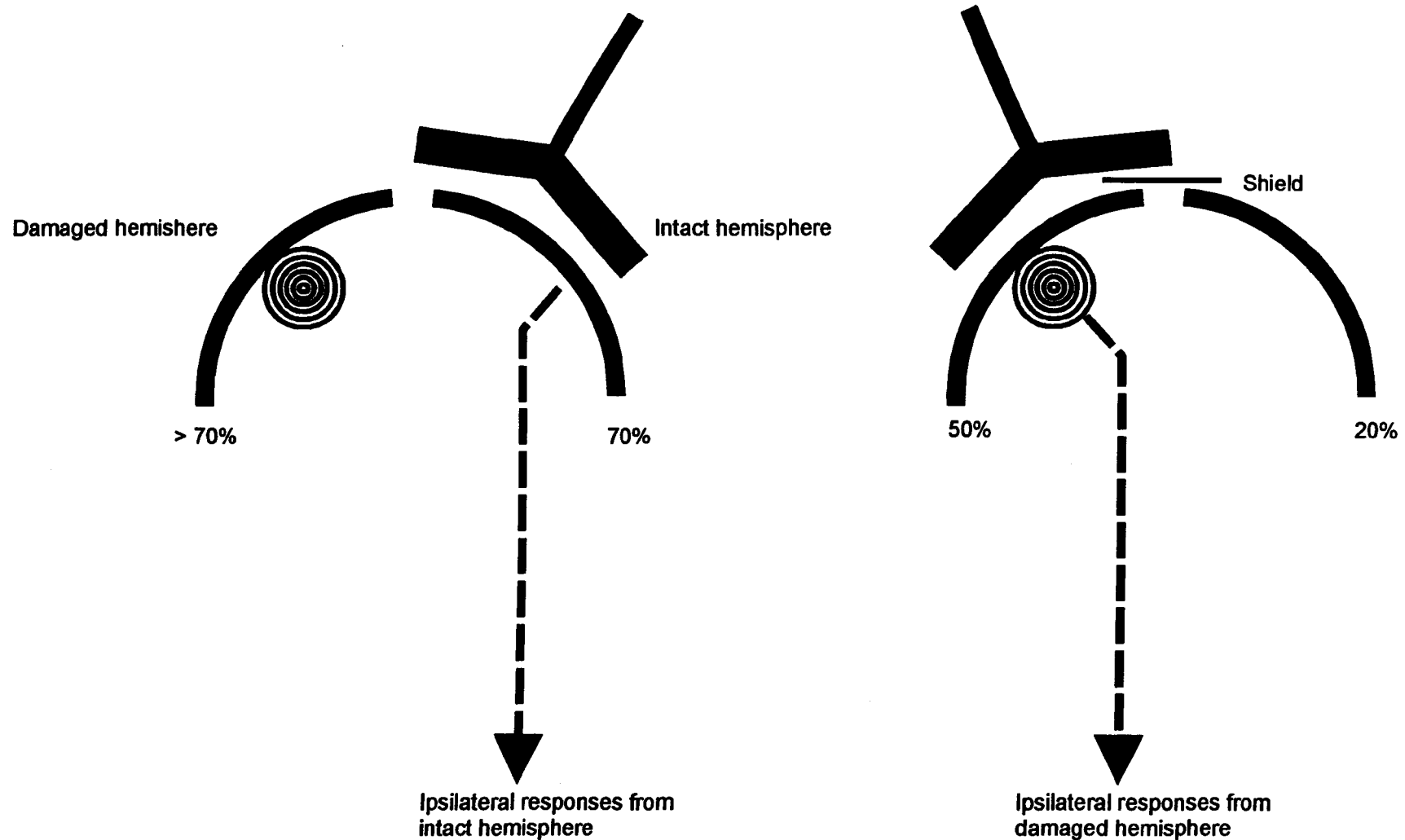


Figure 4.5A Possible spread of excitation to the opposite hemisphere.

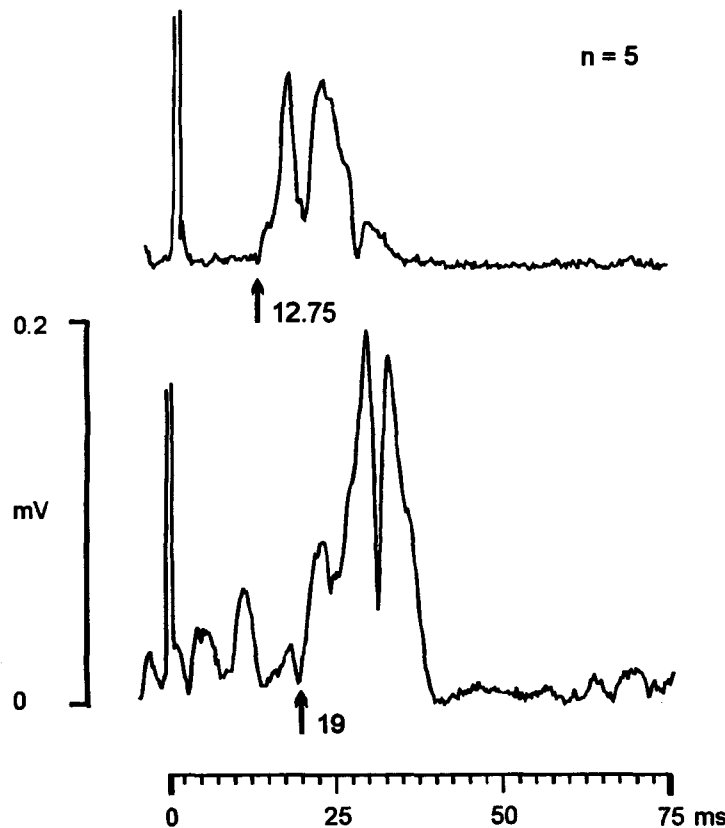
If the intensity of TMS required to evoke a contralateral response from the intact hemisphere is low, (e.g. 20% as in right diagram) then when high intensities are applied to the damaged hemisphere (e.g. 50%), the lateral rim of the coil lying over the intact side, may induce a response, which would be falsely counted as an 'ipsilateral response'. This possibility was prevented by shielding the rim of the coil with an aluminium plate. The plate reduces the field under the rim to <10% of that normally present. In contrast when the thresholds for exciting responses from the damaged hemisphere are high (e.g. >70%), in left diagram) then ipsilateral responses evoked with lower intensities from the intact hemisphere are unlikely to have been due to excitation of the opposite hemisphere.

Stimulation left cortex at 50%

Ipsilateral responses without shield over right undamaged hemisphere

Right hemisphere shielded

Patient FD



Left Biceps

Left EDC

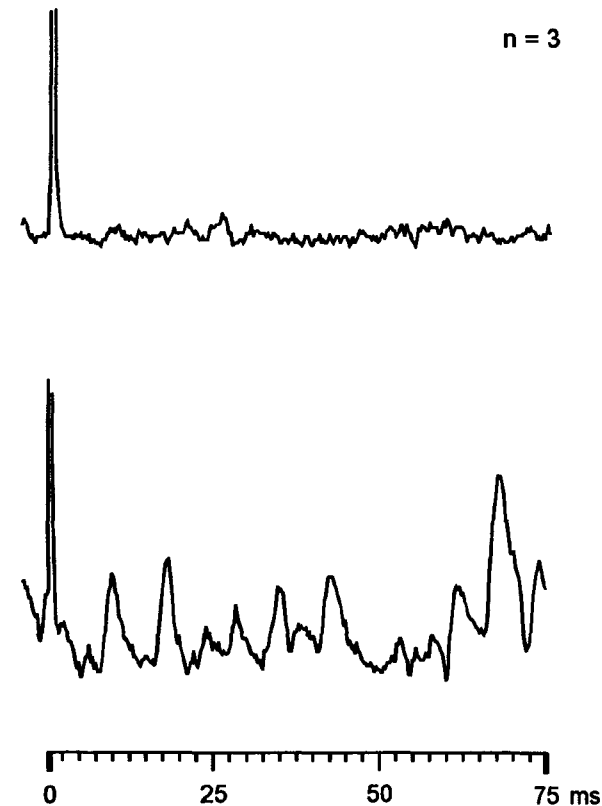


Figure 4.5B Artifactual ipsilateral responses from the damaged cortex.

These responses are from a patient who needed remarkably low stimulus intensities to obtain responses in the unaffected muscles following stimulation of the intact right hemisphere (passive threshold = 20% and active threshold = 17% max. output of the Magstim stimulator). The responses illustrated were obtained from stimulation of the patient's left damaged cortex at 50%: more than twice these low intensities. Large responses were evoked in the muscles on the unaffected (ipsilateral) side. When the right cortex was shielded the responses on the left side were abolished, proving that in this case, these left side responses were not truly ipsilateral.

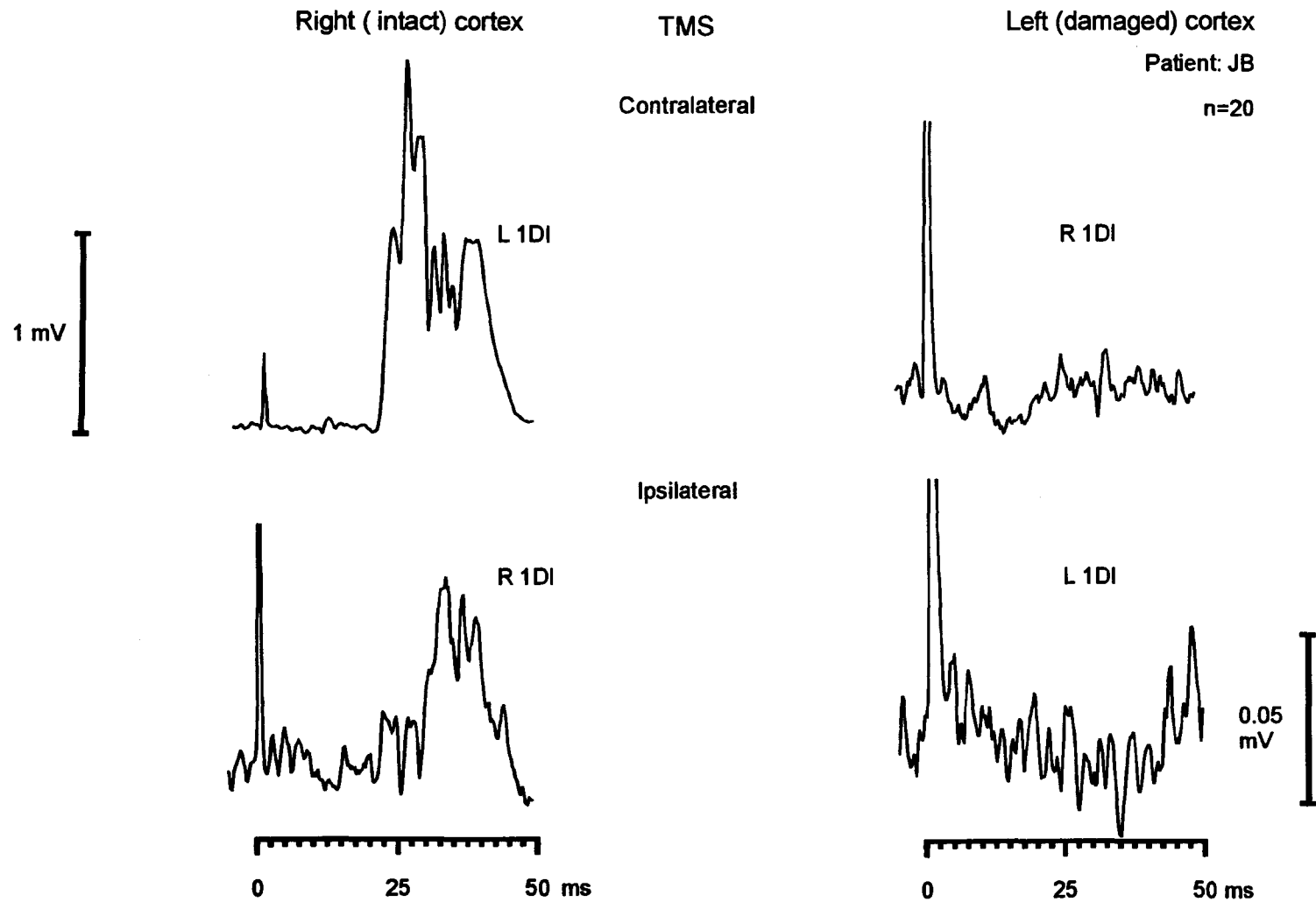


Figure 4.6 Ipsilateral response from the intact cortex.

Averaged (n=20) EMG recordings from 1DI in a single patient during TMS at 70% max. output of stimulator (Digitimer stimulator). Stimulation of the right intact cortex produced a response in the left unaffected 1DI and a small but clear ipsilateral response in the right affected 1DI. No responses were obtained from stimulation of the left damaged cortex. Calibration bar for all records is 0.05 mV, except top left record where it is 1 mV.

4.5 Discussion

4.5.1 Voluntary muscle contraction and the presence of TMS responses

The absence of both voluntary activity *and* a short latency response in a given muscle could be taken to indicate that not only is there considerable disruption of the CS system projecting to the muscle, but also that under normal circumstances, activity in this same system makes a significant contribution to the generation of voluntary activity. However, before concluding that there is significant damage to the CS system, it is important to remember that unless there is sufficient background facilitation within a motoneurone pool, any CS volleys excited by TMS may fail to generate an EMG response. Thus in this study only a small number of cases were found in which a response to TMS was obtained in a silent muscle (our category 2). It is therefore important to make a clear distinction between *absence* of responses to TMS in silent muscles (category 1 responses) and in muscles which could be activated by the patient (category 3). Interestingly, all of the category 3 cases were in proximal arm muscles.

Distal muscles: EDC and 1DI. My results indicate that responses to TMS are always present in stroke patients who have or who recover voluntary contraction of muscles acting on the fingers (EDC and 1DI). Strength of voluntary contraction was significantly correlated with the presence responses to TMS and this correlation was particularly strong for EDC and 1DI.

Proximal muscles: Biceps and deltoid. The results for recovery of proximal muscle activity are less clear. Once again, Group A patients, who had better upper limb motor scores, also had responses to TMS in proximal muscles, but patients from Group B who recovered the voluntary activity in deltoid or biceps did not necessarily have responses to TMS. The ability to move only within the flexor synergy, or to break out of it did not distinguish responders from non-responders. Higher thresholds for proximal musculature may have clouded the results.

My interpretation of these findings is that the integrity of the CS pathway is essential for voluntary activation of distal hand and finger muscles. In the patients who only slowly recovered hand function, some reorganisation of the CS connections must have taken place; responses to TMS generally reappeared just before or at the same as the return of voluntary activity. Conversely the integrity of the CS pathway may not be essential for voluntary activation of proximal muscles. Some patients could activate these muscles, but there was no response to TMS, suggesting that brainstem descending systems must have been mediated the voluntary activity. It is likely that corticofugal control of these systems was also disrupted in the more severely affected patients.

4.5.2 Correlation of hand function with presence of TMS responses.

Patients with immediate recovery of hand function (Group A) showed responses in distal muscles on the first occasion they were tested, while Group B patients either did not show responses until hand function returned, or showed no recovery of hand function and a continued absence of response to TMS. The presence of responses in the more proximal muscles did not show any obvious relationship to the recovery of arm function.

4.5.3 Latency of contralateral responses to TMS and hand function on the affected side.

The latency difference of responses in the same muscle on the affected and unaffected sides was correlated with strength, and this correlation was strongest for the distal muscles, 1DI and EDC. Other authors have found similar correspondence between motor function and response latency for thenar muscles (Dominkus et al. 1990; Hömberg et al. 1991; Ferbert, Vielhaber et al. 1992; Heald et al. 1993b). Abnormally long latencies may arise because of changes at the cortical level (differences in the site and degree of activation), changes in CS conduction or changes in the degree of temporal summation and facilitation needed to activate the target motoneurons. There is experimental evidence (Branston, Bentivoglio, Momma and Symon, 1988) that the more rapidly conducting fibres of the pyramidal tract may be the most susceptible to stroke. Thus the fastest fibres, likely

to mediate the short-latency EMG responses to TMS, are most prone to damage, possibly leaving intact the slower fibres, which make up the vast majority of the CS projection (see Porter and Lemon 1993 p 82). In the monkey, there is evidence that some of these slow fibres also make monosynaptic connections with their target motoneurons (Lemon et al. 1993).

4.5.4 Changes in response latency during recovery from stroke.

Response latency often decreased with time after stroke and this decrease was correlated with MRC score. These results, which confirm the extensive study of Heald et al. (1993b) suggest that there can be substantial recovery within the CS system after stroke. The mechanisms are unclear; obviously the reversal of the phenomena referred to above could occur, leading to faster excitation of CS neurones, recovery of axonal conduction amongst the faster cells, and reduction in spinal delays.

4.5.5 Ipsilateral EMG responses to TMS.

In contrast to the findings reported in chapter three, ipsilateral responses to TMS were found in some patients during the first year after stroke, however they were not common. The ipsilateral responses elicited from the *unaffected hemisphere* are of particular interest, especially in the 15 cases where no responses in the same muscle could be evoked by TMS over the damaged hemisphere. In these cases it is extremely unlikely that the ipsilateral responses arose from inadvertent stimulation of the opposite hemisphere. All of the ipsilateral responses to proximal muscles had latencies which were significantly longer than the normal onset latencies for a response in the homologous muscle on the contralateral side. The pathways responsible are probably quite different from the fast CM projections mediating the short-latency contralateral responses. The intact cortex could access ipsilateral muscles by a number of routes, including ipsilaterally-projecting CS fibres and cortico-reticular projections (Fries et al. 1991; see Lemon 1993b). These pathways appear to be more easily accessible to TMS in stroke

patients. Because of damage to the opposite hemisphere, a transcallosal route would seem unlikely in these patients, although disruption of callosal pathways may change the susceptibility to TMS of other corticofugal outputs emanating from the intact cortex.

There has obviously been some reorganisation of descending projections in the patients of Group B, since 9 'secure' cases of ipsilateral responses in distal muscles were found. Interestingly, three out of five IDI responses had latencies within 2SD of the normal value. A similar observation has been made by Carr et al. (1993) in hemiplegic children who sustained damage at an early gestational age. In these children, several lines of evidence, including the similar latency of the ipsilateral responses, suggested that these responses were mediated by branching of CS axons derived from the intact side.

It is important that most of the ipsilateral responses from the intact side were found in poorly recovered patients (Group B), suggesting that whatever reorganisation of motor pathways has occurred to produce these abnormal ipsilateral responses in the affected limb, this reorganisation has not been of any obvious benefit to this group of patients. Palmer et al. (1992) made a similar conclusion because they could not find any evidence of ipsilateral responses in a group of nine recovered stroke patients. It is a considerable challenge to work out which of the changes in cortical activity (Chollet et al. 1991; Weiller et al. 1993) and connectivity that occur in the unaffected hemisphere are beneficial for recovery.

Ipsilateral responses from the *damaged hemisphere* that were classified as secure (i.e. unlikely to be have been due to inadvertent activation of the healthy hemisphere) were also observed in the patients. In distal muscles, these ipsilateral responses showed rather similar latencies to those evoked on the contralateral side (see table 4.3). Once again this result points to a reorganisation of motor outputs, or at least a change in the susceptibility of these outputs to TMS. Fries et al. (1991), using percutaneous electrical stimulation and TMS, found ipsilateral responses from the damaged cortex at

suprathreshold stimulation in a patient who had suffered a lacunar infarct in the posterior limb of the internal capsule. Latencies were similar or even slightly shorter to those evoked in the same muscle from the unaffected side. Since there was MRI evidence for degeneration of the pyramidal fibres, these authors suggested that indirect cortico-reticulospinal connections were responsible, both for these responses and for the remarkable degree of motor recovery made by this patient. While it is true that similar response latency does not indicate that the same pathway is responsible, it is also the case that the MRI evidence cannot prove that all pyramidal fibres were lost, and it is well known from the animal literature that subtotal pyramidal lesions rarely produce a permanent motor deficit (Lawrence and Kuypers 1968a; Chapman and Wiesendanger 1982).

4.5.6 Conclusions

In conclusion, this study has shown that there are clear differences in the pattern of recovery of responses to TMS in proximal and distal upper limb muscles, and that the presence of these responses correlates well with recovery of voluntary activity in distal muscles, but less well with that in the proximal group. This evidence can be interpreted as confirming the relative importance of CS projections for normal hand function. My results suggest that there may be striking reorganisation of motor pathways after stroke but that not all of these changes assist in recovery of hand function.

CHAPTER FIVE.

THE PRESENCE OF IPSILATERAL RESPONSES TO TMS IN UPPER LIMB MUSCLES OF NORMAL SUBJECTS.

5.1 Summary

TMS produces ipsilateral EMG responses in upper limb muscles of stroke patients, but are these responses the result of pathology? To answer this an investigation of ipsilateral responses in normal subjects was carried out.

Fifteen normal volunteers were tested for ipsilateral responses in proximal and distal upper limb muscles. TMS was delivered using a double cone (DC) coil while subjects made bilateral contractions. Stimuli at intensities of up to twice that of the threshold intensity needed to obtain a contralateral response in the passive 1DI (up to 55% of the max. stimulator output) were delivered. A small butterfly (SB) coil was also used with seven subjects.

Ipsilateral responses were relatively infrequent. In nine subjects, ipsilateral short-latency responses to DC stimulation were observed. Responses were seen in: deltoid, pectoralis major, biceps, and 1DI. Ipsilateral responses in biceps and pectoralis major, but not in 1DI were evoked with the SB coil.

Onset latencies of ipsilateral responses were generally longer than those in contralateral homologous muscles. This was particularly clear for the proximal muscles, where the mean difference was 8.6 ms. The difference was less marked for the responses in 1DI (mean 4.1 ms). Peak amplitudes of ipsilateral responses were typically 5-10 times smaller than contralateral responses. In contracting muscles, the threshold for ipsilateral responses was always higher than for contralateral, by a factor of 1.3 to 2.8. No ipsilateral

responses were seen in relaxed muscles.

Because of the size and position of the DC coil, it is possible that ipsilateral responses were due to inadvertent stimulation of the opposite hemisphere. With a shield in place over one side of the DC coil, the response in the ipsilateral 1DI was abolished, while the ipsilateral biceps responses was unaltered, as were the contralateral responses.

The results confirm the presence of ipsilateral responses to TMS in proximal upper limb muscles in normal subjects. These responses cannot have been due to inadvertent stimulation of the opposite hemisphere because: a) the ipsilateral-contralateral latency difference was too long. b) the responses could be elicited with the more focal butterfly coil. c) the responses were unaffected by shielding the rim of the DC coil lying over the opposite hemisphere. Ipsilateral responses in 1DI to DC stimulation may have been due to activation of the opposite hemisphere. They showed rather similar latencies to those in the homologous contralateral muscle, were not activated by the SB coil and were abolished by shielding the large DC coil.

The ipsilateral responses evoked in the stroke patients in the longitudinal study (see chapter four) were different from those seen in normal subjects in three respects: first, some ipsilateral responses were evoked in distal muscles (EDC and 1DI); second, ipsilateral and contralateral responses sometimes had rather similar thresholds and finally, in some cases contralateral and ipsilateral responses had similar latencies.

5.2 Introduction

During the course of the longitudinal study ipsilateral responses to TMS were found in some stroke patients, particularly in the more severely affected group. Other studies have shown that ipsilateral EMG responses in upper limb muscles can be evoked in patients with unilateral damage to the motor pathways (Benecke et al 1991, Fries et al

1991, Carr et al 1993; Maassen van den Brink, van der Kamp and van Dijk, 1994). Are these responses the result of pathology? It is unclear from the literature whether or not ipsilateral responses exist in normal subjects.

Early TMS studies using a circular coil that was positioned over the vertex demonstrated ipsilateral responses in hand and arm muscles (Meyer, Kloten, Britton and Benecke, 1990; Day et al. 1989; Colebatch et al., 1990). However it is known that a circular coil placed over the vertex is able to activate both hemispheres (Rothwell et al., 1991) and therefore ipsilateral responses may have resulted from spread of stimulating current to the other hemisphere (Meyer et al. 1990). Later studies, using more focal stimulating coils, have shown ipsilateral responses in trunk muscles and the diaphragm (Maskill, Murphy, Mier, Owen and Guz, 1991; Carr et al., 1994), but reports of ipsilateral responses elicited in arm and hand muscles in normal subjects are scarce. Wassermann et al. (1991) observed small, late ipsilateral responses in biceps and deltoid and recently reported responses in 1DI, in six subjects, using an SB coil (Wassermann et al. 1994).

Three groups have reported negative findings. Farmer, Ingram and Stephens, (1990) did not obtain ipsilateral responses to TMS in 1DI in four normal subjects, and Fries et al (1991) reached similar conclusions using electrical stimulation and recording from the thenar muscles. Carr et al., (1994) recording from proximal and distal upper limb muscles also did not find any ipsilateral responses in their sample of twenty one subjects.

It might be expected that ipsilateral responses would be found in proximal or truncal muscles since it is known that the motor cortex can influence proximal muscles through ipsilateral CS fibres and indirectly via bilateral effects upon the reticulospinal system (Nathan and Smith, 1955; Kuypers, 1981). In contrast CS fibres are distributed mainly to contralateral motoneurone pools of distal muscles, so ipsilateral responses are not likely to be found in the hand.

This investigation was carried out to clarify the presence of ipsilateral responses and to determine whether they differed from those found in stroke patients.

5.3 Methods

5.3.1 Subjects

Fifteen normal subjects, (eight of them male) aged 19 - 59 were investigated. Surface EMGs were recorded from deltoid, pectoralis major, biceps and 1DI.

5.3.2 Magnetic stimulation

A Magstim 200 stimulator fitted with a double cone (DC) coil was used. In some subjects the responses to stimulation with a small butterfly (SB) coil were also studied (see chapter 2, section 2.6 for details). The DC coil is designed to fit over the vertex to activate the leg area of the motor cortex, whereas the SB coil is ideal for hemispheric-selective stimulation. This is obviously more suitable for the investigation of ipsilateral responses. However, the greater power and comfortable, stable positioning of the DC coil make it advantageous for producing responses where thresholds are high.

A tight fitting strip of latex worn on the head and secured under the chin allowed sites 3 cm and 6 cm lateral to the vertex on both sides to be marked for consistent coil position. These positions will be referred to as V+3 and V+6 in this report. The DC coil was hand held with the junction region centred over each of the marked positions and special care was taken to maintain its position. At each coil position the threshold stimulus intensity for producing an EMG response in the passive contralateral muscles were recorded. The SB coil was held with the handle approximately orthogonal to the estimated medio-lateral course of the central sulcus and pointing forwards (Davey et al., 1994).

5.3.3 Experimental procedure.

The subject performed a task designed to allow simultaneous contraction of all four muscles bilaterally: The arms were held with the shoulders flexed and adducted towards the midline, the elbows were flexed with forearms supinated and the index fingers were opposed to make pinch grips against the thumbs. While the task was being performed, at least 10 stimuli of intensity 5% above the highest passive threshold (from the four muscles) were delivered at a rate of one stimulus every 3.5-5.0 seconds. However, if this intensity exceeded 55% (of the maximum output of the stimulator), as it did in most cases, stimulation was performed at 55%, to minimise any discomfort. In many cases the intensity used was close to twice the passive threshold of the response in the contralateral 1DI.

If any ipsilateral responses were seen in the average of the recorded sweeps, the stimulus intensity was reduced by 5% then by 10% and further recordings made to determine the active threshold of the ipsilateral responses. The experiment was repeated three times, with the coil centred over each of the marked positions in turn. In three subjects only one hemisphere was investigated.

In thirteen of the fifteen subjects it was determined whether ipsilateral responses could be obtained during performance of the same task, but involving only the ipsilateral limb. In two subjects showing ipsilateral responses in 1DI, and one subject with ipsilateral responses in biceps during the bilateral task, it was determined whether the responses were obtainable during bilateral finger abduction or elbow flexion, i.e. in the absence of voluntary contraction of the other muscles.

In seven subjects in whom ipsilateral responses were observed, attempts were made to elicit the ipsilateral responses, during bilateral contractions, using the SB coil centred over the marked positions at strengths of 80%-100% maximum output.

5.3.4 Shielding current spread to the opposite hemisphere.

Because of the size and position of the DC coil, it is possible that 'ipsilateral' responses were due to inadvertent stimulation of the opposite hemisphere. When the junction region is positioned at 6 cm lateral to vertex on one side, one of the coil rims lies over the motor area of the opposite side. To investigate this a further experiment was carried out with two of the subjects who had ipsilateral responses when the DC coil was used. Ipsilateral responses had been obtained from biceps and 1DI in both of them.

A large 1 mm thick aluminium sheet, was fixed to the coil so as to completely cover the underside of one of the DC coils. Because the fast changing magnetic field or pulse from the coil caused eddy currents to flow within the aluminium sheet it made an effective shield. The induced eddy currents in the sheet of aluminium generate a magnetic field which opposes the pulse from the coil. This has the effect of deflecting much of the magnetic pulse, so that its distribution is considerably modified. In addition a considerable amount of energy was dissipated in the form of noise in the plate which was restrained from moving under the influence of the magnetic field. Search coil experiments showed that the shield reduced the induced current beneath it, at the rim of the coil, to less than 10% of the unshielded value, with only minor changes in field strength at the coil centre.

Assessment of contralateral thresholds in one subject showed that the shield did slightly weaken the effect of the parts of the coil which were unshielded. The thresholds of responses in active muscles were raised by 2% (max. stimulator output) for 1DI and 6% in biceps. Stimuli were delivered at intensities of 55% and 60% during bilateral contractions of the muscles in one subject and at 45% and 50% in the second subject, who was reluctant to allow further increase in stimulus intensity. The reluctance may have been due to the loud noise from the plate. It was startling even though earplugs were worn by both subjects and experimenters.

5.4 Results

5.4.1 *Ipsilateral responses during bilateral contraction*

Although clear responses were nearly always obtainable in contralateral muscles at the strengths used, ipsilateral responses were relatively infrequent. Ipsilateral EMG responses were observed in 9 of the 15 subjects. Examples are shown in figure 5.1. Responses could not always be evoked from both hemispheres in any one subject. Some subjects showed responses in only one muscle, others in several, but no subject showed ipsilateral responses in all muscles. Responses were observed at both V+6 and V+3. Table 5.1 shows the frequency of occurrence of ipsilateral responses in different muscles.

There did not appear to be a difference between the occurrence of ipsilateral responses in muscles of the preferred or non-preferred limb. No relation to handedness could be determined since only one subject was left-handed. No relation between occurrence of the responses and age or sex was observed.

5.4.2 *Latencies*

Figure 5.2 compares the onset latencies of both ipsilateral and contralateral responses in all muscles tested. Responses observed on stimulation at V+3 and V+6 are grouped together since there was no clear latency difference between responses evoked from these sites. Table 5.1 shows the mean latency of the ipsilateral and contralateral responses in each muscle.

For each ipsilateral response, the latency was measured from the average of ten to twelve stimuli and the latency for the contralateral response in the same trial was subtracted. The mean latency difference was calculated, and tested for significance using a two-tailed paired t-test. For the three proximal muscles the mean latency difference was 8.6 ms (± 1.0 SEM), the difference was less marked for 1DI, mean 4.1 ms (± 0.6 SEM). The latency difference was significant for three muscles (pectoralis major $t = 6.2$, biceps

$t = 5.1$ and $1DI\ t = 6.9$, $p < 0.05$). Deltoid was excluded from statistical analysis since only one ipsilateral response was obtained.

5.4.3 Amplitudes

Figure 5.3 shows the size of the ipsilateral responses relative to the contralateral response amplitude that were obtained during bilateral contraction only. Peak amplitudes of contralateral responses were typically 5-10 times larger than the ipsilateral responses. Unfortunately it was impossible to control the level of background EMG in these experiments since this would have required the use of feedback for eight muscles simultaneously, or else the investigation of each muscle pair in turn, which would have quadrupled the number of stimuli required and the length of each experiment. It is known that the size of the background EMG affects the response amplitude (Hess, Mills and Murray, 1987). However accepting there was probably variation in the amount of activation facilitating the responses in different muscles and in different subjects, ipsilateral responses were always smaller than the contralateral responses, with only one exception.

5.4.4 Thresholds

Passive thresholds for *contralateral* responses in 1DI were lower than for the other muscles and in accord with the human motor homunculus demonstrated by Penfield and Boldrey (1937) they were higher at the more medial site, (V+3) than at V+6. Mean passive thresholds at V+6 was 27.8 (S.D. ± 5.69) and at V+3 32.0 (S.D. ± 7.3). Thresholds for pectoralis major were the highest with many subjects having thresholds that were greater than the highest test intensity of 55% (max. output). When exact threshold intensities could be determined they were lower at V+3 than at V+6 (mean 40.5 (S.D. ± 7.2) at V+3 and 44.4 (S.D. ± 6.4) at V+6).

Contralateral

Ipsilateral

n=12

Pec.Major

0.35mV

Biceps

0.6mV

1DI

4.91mV

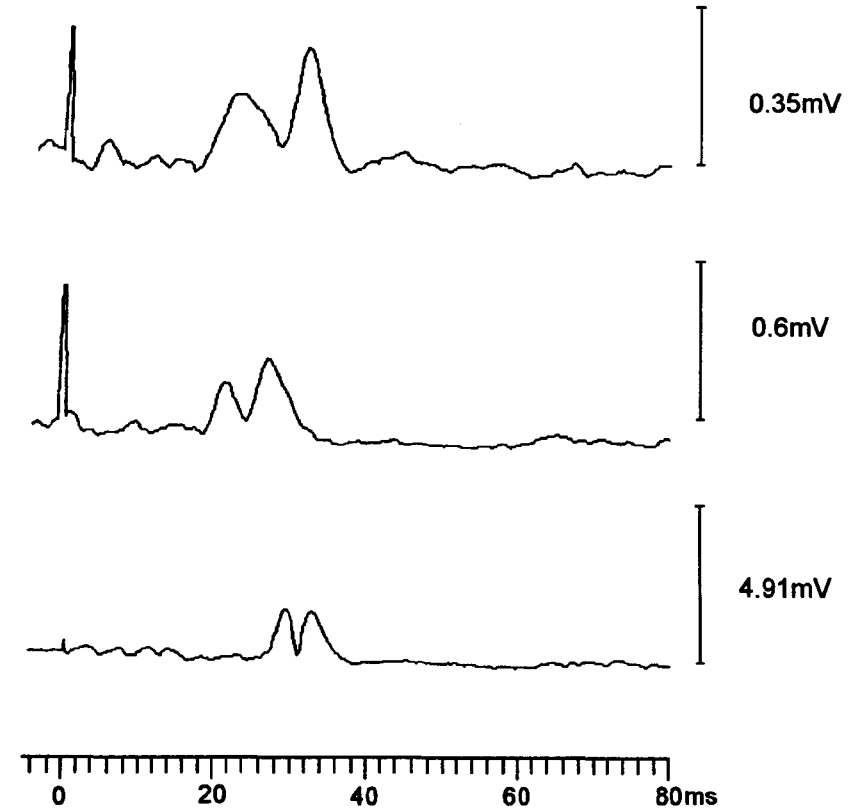
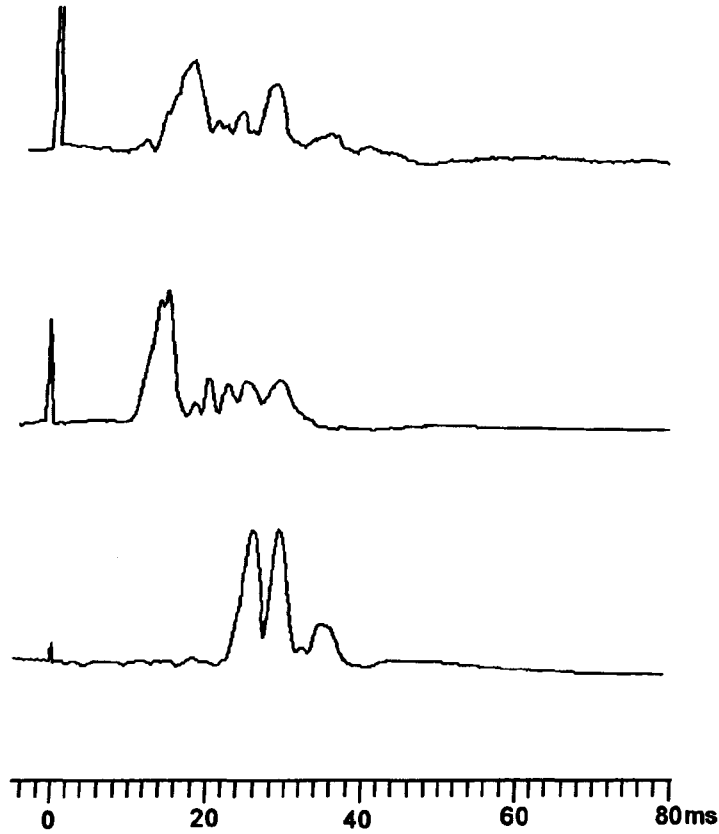


Figure 5.1 Ipsilateral responses in normal subjects

Examples shown of pectoralis major and biceps responses are from the same subject. 1DI responses are from a different subject. Vertical scales are comparable for each muscle pair.

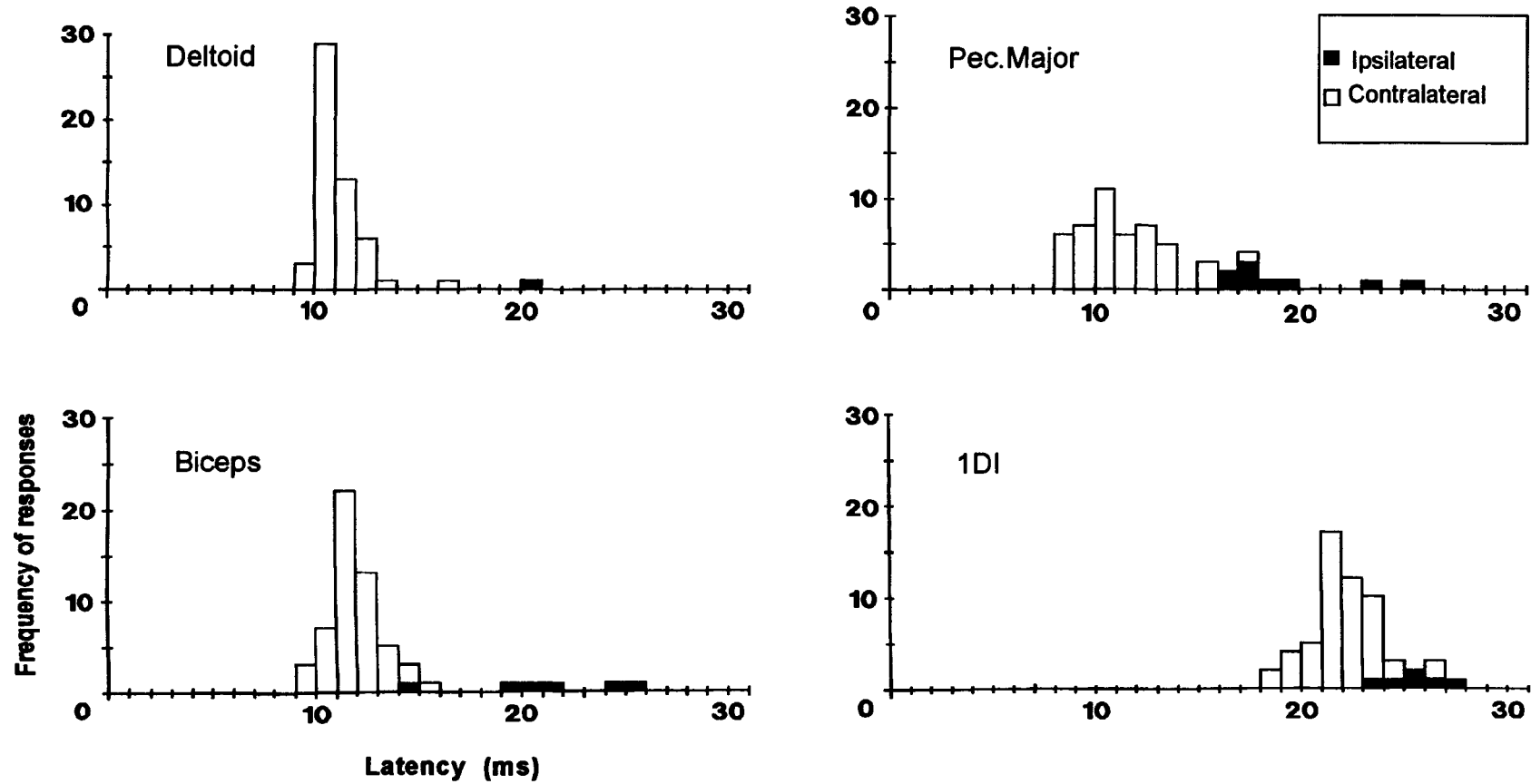


Figure 5.2 Response latencies in four upper limb muscles recorded from 15 subjects.

Ipsilateral responses are generally later than contralateral responses although there is some overlap particularly in 1DI.

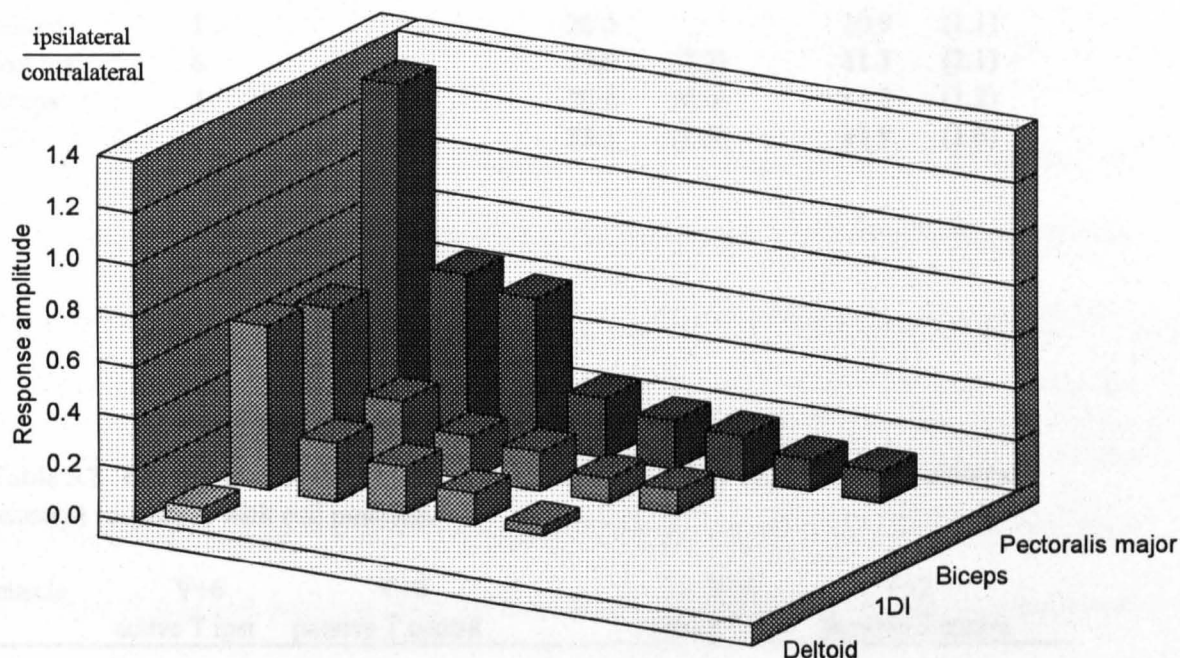


Figure 5.3 Relative amplitudes of ipsilateral responses.

Response amplitudes were calculated by subtracting the mean background amplitude from the amplitude of the largest peak in response. The relative amplitude for a given muscle was calculated by dividing the ipsilateral by the contralateral value. The points shown for a particular muscle represent responses from different subjects. Except in one case for pectoralis major, the ipsilateral responses were of smaller amplitude than the contralateral responses.

Table 5.1 Frequency and latency of ipsilateral responses, latency of contralateral responses for comparison.

muscle	subjects (total =15)	hemispheres	mean (S.D) response latencies in ms			
			ipsilateral		contralateral	
deltoid	1	1	20.0		10.9	(1.1)
pect maj.	6	9	19.0	(3.2)	11.3	(2.1)
biceps	4	6	20.8	(4.0)	11.8	(1.2)
1DI	5	6	25.3	(1.5)	21.9	(1.6)

Table 5.2 Comparison of threshold intensities for ipsilateral (ipsi) and contralateral (contra) responses with coil position.

muscle	V+6	V+6	V+3	V+3
	active T ipsi	passive T contra	active T ipsi	passive T contra
deltoid			46	29
pect maj.	37	42	30	45
	40	40	50	>55
	50	40	40	53
	<30	40		
	40	>55		
	40	50		
biceps	27	32	45	26
	40	25	<40	40
	40	36		
	34	26		
1DI	37	26		
	40	25		
	40	24		
	30	25		
	40	23		
	39	24		

Table 5.2 compares the active ipsilateral and passive contralateral thresholds in any one subject at any one stimulation position. Ipsilateral responses were not observed when the ipsilateral side was relaxed. For 1DI the active thresholds for ipsilateral responses were always higher than the contralateral passive thresholds. For pectoralis major and biceps there was some overlap between the ipsilateral active and contralateral passive thresholds; the only response seen in deltoid had a very high threshold. Thresholds from stimulation of either hemisphere are combined since there was no difference between these. It must be borne in mind that the ipsilateral active thresholds were determined from averages and the contralateral passive thresholds from single sweeps post hoc. during the experiment. Small responses are more easily detected during data analysis, so the difference in thresholds is likely to be underestimated in table 5.2. As can be seen from this table, it was not possible to determine exact active thresholds for all the ipsilateral responses since recordings were seldom carried out at a strength at which exactly three responses were seen out of ten. It can also be seen that it was not possible to examine all subjects at both V+3 and V+6.

Since voluntary contraction lowers the response threshold, the difference between active thresholds for ipsilateral and contralateral responses would be even greater than the difference between active ipsilateral and passive contralateral thresholds. In an experiment to confirm this view exact active thresholds were determined in five subjects, for both the ipsilateral and contralateral responses in 1DI, biceps and in one case deltoid (see table 5.3). The active threshold for ipsilateral responses was always higher than for contralateral, by a factor of 1.3 to 2.6. The mean threshold difference for the nine observations was 24.6%.

5.4.5 Ipsilateral responses during variations of the task.

Examples of ipsilateral responses in all muscles were obtained during performance of the unilateral task, ipsilateral to the stimulated hemisphere. Responses were seen in seven of the thirteen subjects tested. Responses were obtained from seven hemispheres (five subjects) in 1DI, four in biceps (three subjects), five in pectoralis major (three subjects) and one in deltoid. Ipsilateral responses were seen in some subjects on performing the ipsilateral task only, in others on performing the bilateral task, and in others under both conditions.

Ipsilateral responses in 1DI were clear in two subjects when bilaterally abducting the index fingers. Another subject, who showed ipsilateral responses in biceps, still showed these responses when performing only an elbow flexion with the forearms supinated. It would appear from these results that ipsilateral responses can occur irrespective of the task in which the muscle is involved.

5.4.6 Repeat tests

Six subjects were tested on at least two occasions; this allowed an estimation of the repeatability of the responses. In most cases the subjects still showed ipsilateral responses in the same muscle on the second testing (except that two subjects had responses in pectoralis major in the second test but not the first). However, the response was not always obtained under exactly the same conditions (bilateral versus unilateral task; V+3 versus V+6; different stimulation intensities).

5.4.7 Ipsilateral responses obtained using the SB coil

Four subjects, all of whom showed ipsilateral responses in 1DI if the DC coil was used were subsequently tested with the SB coil. In these subjects, ipsilateral responses of latencies similar to those previously seen in 1DI could not be produced using the SB coil even at 100% intensity. Although at this strength the contralateral response obtained was

large, response thresholds were substantially higher for the SB coil than for the DC coil. Ipsilateral responses might not be detected when using the SB coil for this reason. This question was addressed by measuring the amplitude of the contralateral response obtained using the SB coil and then estimating whether an ipsilateral response would have been observed on the basis of the relative contralateral and ipsilateral amplitudes found when using the DC coil (see table 5.4). This analysis demonstrated that the SB coil was not "powerful" enough to generate an ipsilateral response in 1DI in two of the four subjects.

Ipsilateral responses in biceps could be obtained with the SB coil in the four subjects who had previously had ipsilateral responses when the DC coil was used. Responses latencies ranged from 18.5 ms to 24 ms. Figure 5.4. illustrates an ipsilateral biceps response from stimulation using the SB coil in one subject. Ipsilateral responses in pectoralis major were obtained with the SB coil in one subject, latency 8.8 ms. No ipsilateral responses were obtained in deltoid using the SB coil.

5.4.8 Ipsilateral responses obtained using the DC coil with aluminium shield.

Responses in 1DI that were obtained with the DC coil positioned over the ipsilateral hemisphere, were abolished when the aluminium plate was in place over the contralateral cortex. This was the case for both subjects who were tested with the shield. However ipsilateral responses in biceps persisted in one subject who received stimuli at the higher intensities of 55% and 60% (see figure 5.5), and lost in the other subject who received lower intensity stimuli of 45% and 50% max. output. With the diminishing effect of the shield on the strength of magnetic field from the coil, these stimuli were probably just below threshold for obtaining an ipsilateral response in biceps from this subject (This subject's threshold for ipsilateral responses in biceps in previous experiments was 40% max. output without the aluminium shield).

Table 5.3 Comparison of active thresholds (T) for ipsilateral and contralateral responses in 5 subjects.

muscle	subject (hemisphere)	active T % max. output stimulator	
		ipsilateral	contralateral
1DI	1(L)	38	18
	1(R)	33	26
	2(L)	54	24
	3(L)	43	20
	3(R)	50	19
biceps	3(L)	52	24
	3(R)	55	20
	4(R)	50	26
deltoid	5(L)	55	32

Table 5.4 Amplitudes of contralateral and ipsilateral responses in 1DI obtained using the DC coil at 50-55% max. output and amplitudes of contralateral responses obtained with the SB coil at 90-100% max. output. *Ipsilateral response amplitudes predicted not observed using the SB coil.*

subject	DC amplitudes (mV)		DC Ratio ipsi/contra	SB amplitudes (mV)		
	contra	ipsi		contra	<i>ipsi predicted</i>	background EMG
1	3.166	0.118	0.04	1.070	<i>0.040*</i>	0.030
3	4.690	3.000	0.64	2.990	<i>1.913</i>	0.234
6	0.533	0.063	0.12	0.156	<i>0.018*</i>	0.015
7	3.184	0.569	0.18	2.817	<i>0.503</i>	0.028

** ipsilateral response amplitudes predicted for SB coil would be too small to be detected against the mean background EMG.*

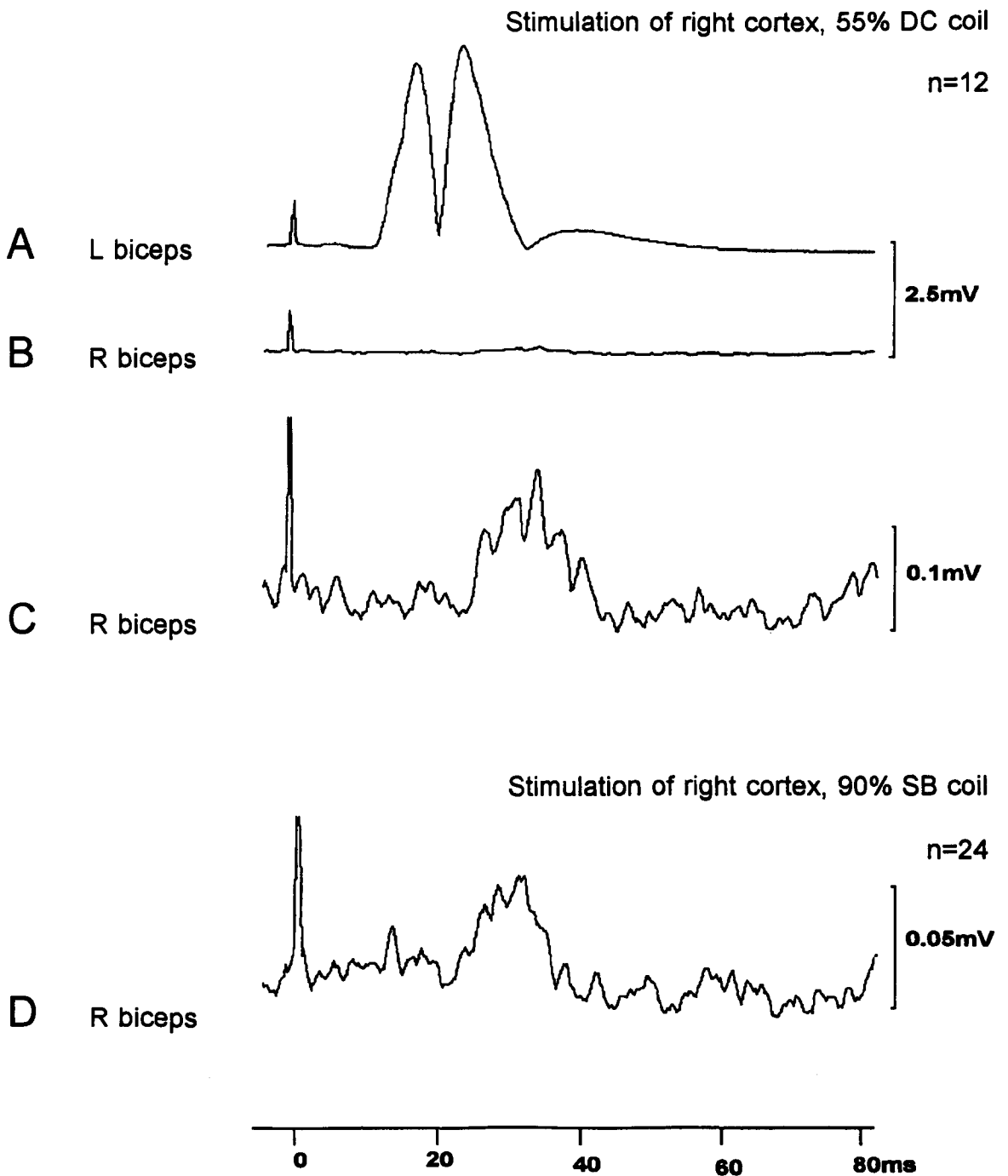


Figure 5.4 Ipsilateral responses in biceps from a single subject using the DC and SB coils.

- A: Contralateral response obtained using the DC coil.
- B: Corresponding ipsilateral EMG (same scale).
- C: The same ipsilateral response as in B, at higher gain.
- D: Using the SB coil, ipsilateral responses were still obtainable from biceps.

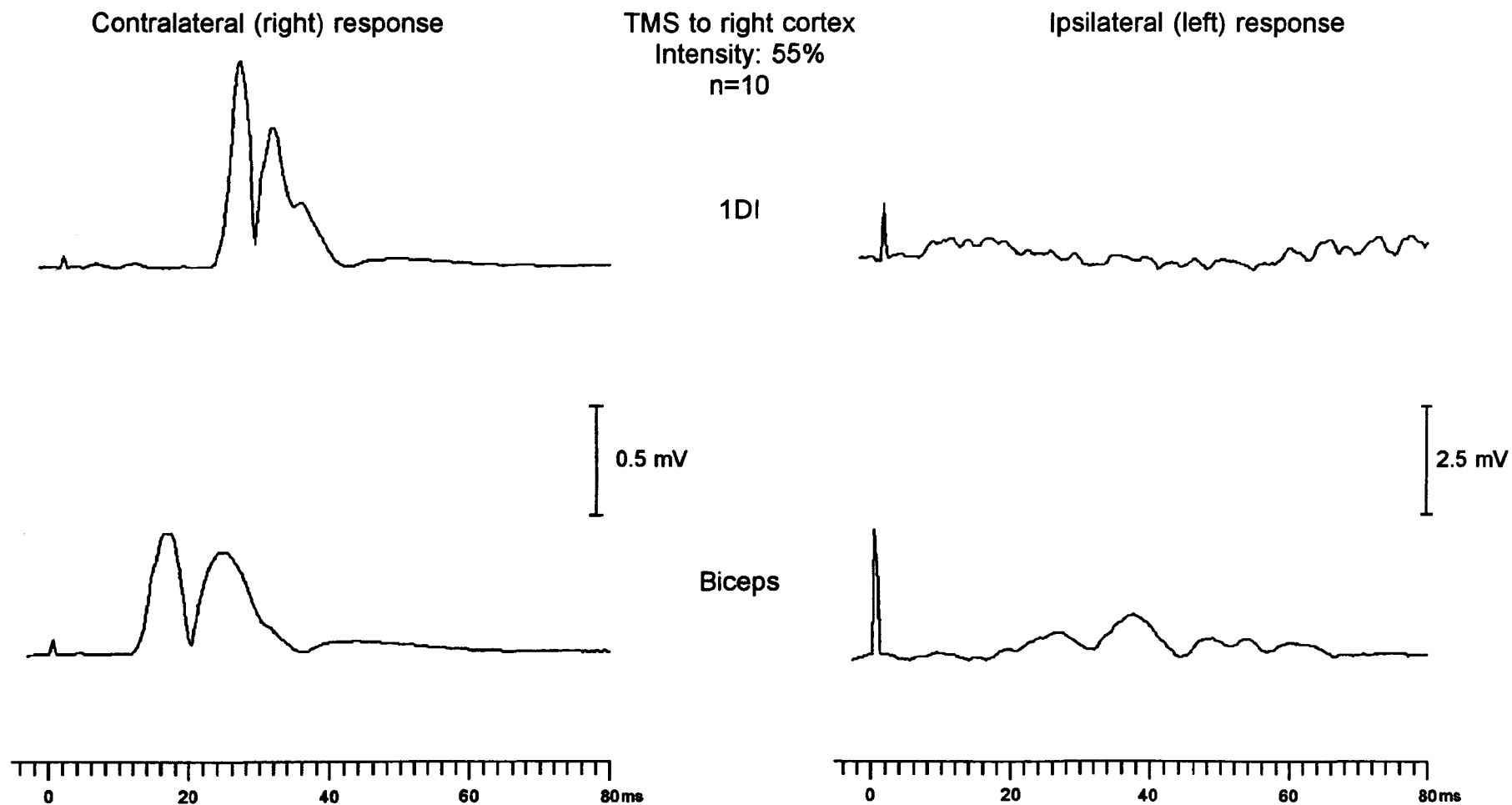


Figure 5.5 Response in 1DI and biceps with shield over left cortex in a single subject.

Ipsilateral response is present in biceps, but not in 1DI. Note different scales for contralateral and ipsilateral responses.

5.5 Discussion

5.5.1 *Ipsilateral responses to TMS are present in proximal upper limb muscles of normal subjects.*

The results confirm the presence of ipsilateral responses to TMS in proximal upper limb muscles in normal subjects. In agreement with the findings of Wassermann et al. (1991) these responses were obtained relatively infrequently at high stimulation strengths and were characteristically smaller and later than contralateral responses to proximal muscles. In my study fifteen subjects were investigated, stimulating at two positions on both hemispheres in most subjects, and recording from four pairs of muscles. At least ten stimuli were given at high strength. The rare occurrence of ipsilateral responses makes it quite likely that they would not be observed in less extensive studies than this one.

Inadvertent activation of the opposite hemisphere can be ruled out as a cause for these proximal muscle responses by consideration of three of our findings: First the ipsilateral-contralateral latency difference, at around 8 ms, is too long. Secondly, responses could be elicited with the more focal SB coil in cases where thresholds were low enough. Thirdly responses in biceps in one subject were unaffected by shielding the part of the double-cone coil lying over the opposite hemisphere. The ipsilateral responses were seen only in active muscles, but there was no general task dependence.

According to Kuypers (1973) *"...contralaterally each hemisphere has full control over the movements of the arm, hand and fingers, while ipsilaterally it has full control over only proximal arm movements and complex arm-hand movements..."*. Ipsilateral responses in the proximal arm muscles could be mediated by at least three separate pathways: Slow CS fibres with a conduction velocity approximately one third of the fast fibres might mediate the ipsilateral responses. The ipsilateral CST arises from a large cortical area and consists of small diameter neurones (Kuypers, 1981). The projections are

far less numerous than the contralateral ones. As a proportion of the corresponding contralateral populations it is estimated that ipsilateral projections from area 4 comprise only 6%, and from area 6 only 2% (Toyoshima and Sakai, 1982). The small number and fibre size would be more difficult to excite using TMS, thus higher response thresholds and smaller amplitudes would be expected. Such a small population of neurones may need repetitive firing to create enough excitation to discharge the motoneurones, so increased onset latencies would also be expected. The variability in occurrence of ipsilateral responses within the population could be explained partly by different amounts of decussation of the CST in the medulla (Nathan and Smith, 1955) and at segmental levels (Kuypers, 1981). In addition the CS distribution of cells giving rise to the ipsilateral and contralateral tracts is unclear; if these differ, the orientation and position of the fibres in each group could affect their potential to be excited by TMS. When threshold is determined from EMG responses, it will also depend upon the strength of synaptic connections made by the CS elements excited by TMS. A further consideration is whether the projections are monosynaptic, or oligosynaptic, since in the latter case the latencies would be both longer and more variable.

Ipsilateral responses could result from transcallosal activation. The corpus callosum is known to contain fibres connecting homologous areas of the motor cortex, although the situation is less clear for the hand areas (Gould, Cusick, Pons, and Kaas, 1986; Rouiller, Babalian, O'Kazennikov, Moret et al., 1994). Recording from 1DI and biceps, Ferbert, Priori et al., (1992) showed transcallosal inhibition of the motor cortex, sometimes preceded by facilitation, in the biceps response to TMS. Some of the ipsilateral-contralateral latency differences seen are appropriate for this route.

A third means of mediation might be through activation of ipsilaterally descending pathways from the brainstem which are activated by cortical stimulation, e.g. reticulospinal pathways.

5.5.2 Ipsilateral responses in 1DI were due to inadvertent excitation to the opposite hemisphere.

The ipsilateral responses in 1DI to DC stimulation look likely to have been due to activation of the opposite hemisphere. The responses showed rather similar latencies to those in the homologous contralateral muscle. Latency differences of up to 5 ms could be explained by indirect activation of CS cells of the opposite hemisphere by the coil rim (Edgley et al., 1990). If the DC coil induces some current into the opposite hemisphere it can be expected that the first muscles to show "ipsilateral" responses would be those with the lowest threshold, such as 1DI. Additional evidence suggesting that the responses in 1DI were not genuinely ipsilateral is that these responses were not seen with the coil centred at V+3, when the rim of the DC coil would have been over the contralateral ear, nor were they observed in response to stimulation with the SB coil and they were abolished by shielding the large DC coil.

This result is not surprising since there is little anatomical evidence for ipsilateral projections to distal musculature (Kuypers, 1981). Branched CS axons are thought to be characteristic in certain pathologies (Farmer et al, 1990, Carr et al, 1993) in which mirror movements are observed, but there is no evidence for significant projections of this type to upper limb muscles in healthy subjects.

Wassermann et al. (1994) are the only group who, having taken precautions to prevent spread of excitation to the opposite hemisphere, have reported ipsilateral responses in 1DI. These were found predominantly from stimulating over an area more lateral than the optimum position for contralateral responses, nearer to a site that was found to

represent a contralateral face muscle (risorius). This finding bears similarities to the findings of an intracortical microstimulation experiment and mapping study in monkeys, in which cells in a subregion of motor cortex, located between the digit and face representations, exhibited activity before and during ipsilateral digit flexion movements (Aizawa et al., 1990). It is possible that true ipsilateral responses were not found in 1DI in my study because the coil was not positioned laterally enough.

5.5.3 Ipsilateral responses in stroke patients are different from those found in normal subjects.

This investigation has produced a more conclusive analysis of the occurrence of ipsilateral responses to TMS in normal subjects and therefore provides a better basis for comparison and interpretation of the ipsilateral responses found in stroke patients. Although ipsilateral responses were not particularly widespread in the stroke patients (chapter 4) they departed from the normal pattern in three ways: first, some ipsilateral responses were observed in distal muscles (EDC and 1DI); second, ipsilateral and contralateral responses sometimes had rather similar thresholds and finally, in some cases contralateral and ipsilateral responses had similar latencies. These differences may result from the enhancement of transmission in these pathways, rather than the development of novel connections. In stroke patients the presence of ipsilateral responses did not correspond to good recovery of hand function. At present it is not possible to determine the nature of change that any ipsilateral reorganisation may bring about.

CHAPTER SIX.

THE CONTRIBUTION OF CS INPUT TO THE PRODUCTION OF FORCE IN PROXIMAL MUSCLES IN NORMAL SUBJECTS AND STROKE PATIENTS.

6.1 Summary

It is well known that the CS system exerts more influence over the activation of distal muscles than proximal muscles. If voluntary activation of proximal muscles is more dependent on inputs other than the CST, then recovery of arm movement after stroke could be explained by a greater facility of these inputs to compensate for loss of CS connections to the motoneurons of proximal muscles, than to those serving more distal hand muscles. Two investigations were carried out to provide a quantitative comparison of the contribution of CS inputs for voluntary activity in proximal and distal muscles of normal subjects. The first demonstrated differences in the rate of increase in EMG response amplitudes to TMS in 1DI, biceps and deltoid with voluntary contraction. In the second investigation the recruitment of low threshold motor units in 1DI and deltoid by TMS was compared. The results confirmed that the differences in facilitation of surface EMG responses by voluntary effort could be explained by differences in CS input to the motoneurons, rather than by the contribution made by other inputs or by differences in the modes of force production between muscles. These two investigations served as a basis for further testing of deltoid responses in three patients. In two of the patients smaller responses to TMS were obtained on the affected side than on the unaffected side during the production of equivalent voluntary contractions, suggesting that the muscle activity was achieved with less than normal CS input to deltoid motoneurons.

6.2 Introduction

The longitudinal study of recovering stroke patients suggested an interaction between the degree of recovery in the ability to contract a muscle under voluntary control, and the responses to TMS in that muscle. The results suggested a very clear cut relationship for the more distal muscles, while there was, in some patients a rather clear dissociation between voluntary effort and response to TMS in proximal muscles. These results prompted a more detailed investigation into how these two factors interact.

It is generally recognised that the CS system exerts more influence over distal than over proximal muscles. This has been demonstrated both physiologically (e.g. Palmer and Ashby, 1992) and by examining the distribution of weakness in the upper limbs of hemiparetic patients (Colebatch and Gandevia, 1989). In healthy subjects, EMG responses to TMS have higher thresholds, smaller amplitudes and are generally more difficult to elicit in proximal than in distal muscles.

One of the features of responses in more proximal muscles is that they are sometimes impossible to elicit unless the subject provides some background facilitation. It has long been recognised that there is a striking facilitation of responses by voluntary activation in all muscle groups. In theory both cortical and spinal mechanisms could contribute to such facilitation: at the cortical level, it is easier to discharge CS neurones if they are active (Baker, Olivier and Lemon, 1994, 1995), while the excitatory impact of any descending CS volley will discharge more motoneurones if these are already active or close to threshold. However, most of the evidence suggests that the spinal mechanisms are by far the more important (Day et al., 1987; Maertens de Noordhout et al., 1992).

In the longitudinal study of stroke patients we attempted to distinguish between cases in which the absence of a response to TMS was due to lack of facilitation of the motoneurone pool (which, as pointed out above, is even seen in the proximal muscles of some healthy subjects) and those cases in which there was no significant CS volley. Thus

98 instances of a category 1 response, in which neither EMG responses nor voluntary activation were present were found, but 25 instances of category 3 responses, clear voluntary EMG, but no response to TMS were also found. All of the latter were observed in proximal muscles.

The observations outlined above lead to the prediction that the contribution of the CS system to the level of voluntary activation will be greater for distal than for proximal muscles. What is needed is a quantitative measure of this contribution. The response to TMS at various levels of contraction may provide some insights into the importance of CS input to the motoneurone pools and activation of different muscles. One problem in making comparisons of the cortical contribution of voluntary activity in different muscles is that they vary in their mode of force production. For example in small hand muscles all the motor units have been recruited by the time the activity has reached 40% MVC. Any further increase in force is dependent on rate modulation (Milner-Brown, Stein and Yemm, 1973; Kukulka and Clamann, 1981; DeLuca, Lefever, McCue and Xenakis, 1982). In contrast large proximal muscles rely much more on recruitment to build up force (Kukulka and Clamann, 1981; DeLuca et al., 1982). In deltoid, new units may be recruited up to 80% MVC. Any differences in the cortical contribution to the amount of activity in large proximal arm muscles and small muscles may be obscured by the properties of their spinal motoneurone pools and these have to be considered in analysing results.

Hess and Mills (1986), and Bawa and Lemon (1993) have demonstrated that TMS is able to recruit motoneurons in an orderly fashion and in the same rank order as can be found for activation under voluntary conditions. This important finding means that differences in the firing probability of a given motor unit that are produced by increasing the intensity of TMS probably reflect the importance of CS input to the different motoneurone pools. If the level of voluntary contraction associated with recruitment of additional units is known, then the importance of CS input for the production of force

may be compared between muscles.

My investigation comprised a series of three experiments: The first demonstrated differences in the rate of increase in EMG response amplitudes to TMS in 1DI, biceps and deltoid with voluntary contraction in normal subjects. The second experiment, in which low threshold motor units in 1DI and deltoid were recruited by TMS confirmed that the differences in facilitation by voluntary effort could be explained by differences in CS input to the motoneurons. These two experiments served as a basis for further testing of deltoid responses in three patients in which voluntary effort and responses amplitudes from the affected and unaffected muscles were compared. The results help to explain the apparent dissociation of voluntary activation and contralateral responses in recovered proximal muscles that was seen in the main study.

6.3 Methods

6.3.1 Subjects

Sixteen normal subjects, (seven of them male) aged 20 to 57 and three patients participated. Twelve subjects took part in the first experiment, i.e. facilitation by voluntary activation. Three of the same subjects (subjects 1,2, and 4) plus the remaining 4 volunteers, participated in the motor unit experiment.

6.3.2 Surface EMG recordings

The normal subjects' surface EMGs were recorded from middle deltoid, biceps and 1DI on the right side. Three subjects who were left handed, had EMGs recorded from the left side. EMG recordings from both affected and unaffected middle deltoids were taken from the patients. Sweep length was 160 ms in the first experiment and 100 ms in the motor unit experiment. The surface EMG gain was increased to x2000 during some of the motor unit recordings to allow easier determination of the percentage of MVC during the voluntary activation of single motor unit and multiple units.

6.3.3 Motor unit recordings

Single motor unit (SMU) activity was recorded from the subject's preferred 1DI and deltoid (i.e right side in 4 subjects, left side in 3). The subject's MVC was sampled before SMU electrodes were inserted. SMU activity was recorded with fine (50 μ m diameter) stainless steel recording electrodes fixed in a 27g hypodermic needle. The recordings were amplified (x500), without rectification and digitised at 20 KHz.

6.3.4 Magnetic stimulation

The best coil position, judged by threshold and amplitude, for obtaining a response in the active right deltoid was found and then marked on the head with red chinograph pencil. The coil was then secured to the head in this position. The lowest stimulus intensities needed to produce an EMG response in each muscle, first in the relaxed state and then with a gentle background contraction, were found.

For the first experiment stimuli were delivered in most cases at 3% (of max. stimulator output) above the passive threshold in each muscle. In three subjects the test stimulus used for 1DI was the same as the passive threshold. In these cases stronger intensities yielded large response amplitudes even without voluntary facilitation and I wanted to avoid obtaining supramaximal responses that would mask any effects of voluntary facilitation. In another three subjects threshold intensities were used to test biceps because stronger stimuli would have been too uncomfortable. For the patient studies the TMS coil was positioned first in the best place to get a response in the unaffected deltoid. Since it was expected that responses would probably not be obtained at rest when the affected side was tested, the stimulator was set 3%-7% (max output) higher than the active threshold; but a ceiling of 50% (max. output) was put on the stimulation intensity to keep the TMS bearable. One patient, JB, had a particularly large difference in active thresholds between sides. In his case the unaffected side was tested a second time using a stimulus strength that was equal to that used for the affected side.

In the motor unit experiments three to five different intensities were used, the lowest being sufficient to discharge an identifiable low threshold SMU with a probability of around 0.25, the highest being sufficient to discharge additional motor units. Care was taken not to stimulate at intensities that were high enough to cause a muscle twitch that was sufficient to disturb the recording needle. The stimuli were delivered in pseudo-randomised blocks of intensities with 25 sweeps in each block.

6.3.5 Experimental Procedures

The subject was seated in a chair with arms, in front of a table. In the first experiment and in the patients' tests, the subject was required to contract each muscle isometrically in turn. Middle deltoid was contracted by abducting the shoulder to about 45°, against the resistance afforded by a strap secured to the back of the chair and wound loosely round the arm above the flexed elbow. Normal subjects were also asked to contract 1DI and biceps. To test 1DI the hand was placed on a board with the index finger and thumb positioned between padded blocks. The subject produced isometric abduction by pressing the side of the index finger against one of the blocks. For the biceps contractions the subject's forearm was restrained by a strap at the wrist. The forearm was supinated and the elbow was flexed at about 120°.

Subjects were required to contract the test muscle maximally, so that visual feedback could be set up for contractions of 5%, 10%, 20% and 50% of the MVC. MVCs for each muscle were collected for 10 sweeps at the beginning of the experiment and then again at the end as a check for consistency.

The subject was asked to maintain contractions at a required percentage of MVC while stimuli were delivered in blocks of 20, with one stimulus every five seconds. The contraction levels were performed in an order designed to minimise fatigue. The order was: 0% (rest for 40 stimuli), 50%, 5%, 20%, 10%, 20%, 5%, 10%, 50%. This procedure was then repeated for the other muscles. The order in which muscles were tested was

varied between subjects. The patient's unaffected deltoid was tested before the affected side.

For the motor unit experiment the subject was asked to contract the muscle very gently to recruit a clearly identifiable SMU; this is referred to as SMU#1. Both audio and visual feedback was given to assist the subject to maintain the firing rate at approximately 10 impulses per second. Fifty sweeps of SMU activity were collected and then the subject was asked to contract a little harder so that a steady discharge of an additional unit (SMU#2) was picked up by the recording electrodes. Fifty sweeps were recorded at this level of contraction. During the delivery of TMS the subject was required to contract so as to discharge SMU#1 alone at a steady rate of around 10 impulses per second. The waveform of the SMU was checked periodically to ensure that the same unit was being activated throughout the test. A satisfactory recording was defined as a run in which the unit's firing had been recorded without loss during the delivery of 40 stimuli at three, four or five different intensities of TMS (total around 200 stimuli).

In two subjects additional confirmation of the stability of the SMU recording was provided by motor unit-triggered averages that were collected continuously throughout the experiment. To do this the intramuscularly recorded potential was discriminated with a double time-amplitude window discriminator. Its output was used to trigger a computer while SMU and unrectified surface EMG data were digitised on two A-D channels at a rate of 10 kHz. The wave form resulting from averaging surface EMG has been referred to as the motor unit-triggered average (MU-TA; Lemon, Mantel and Rea, 1990). The motor unit action potential recorded with an intramuscular needle reflects predominantly the activity of a few muscle fibres of the active motor unit and can change in shape and size during long recording periods. The MU-TA reflects activity of all muscle fibres of the motor unit and remains constant over the period of the recording.

At the end of the experiment, the surface EMG during levels of effort equal to

discharge of SMU#1 and SMU#1 and #2 were again recorded. After the removal of intramuscular electrodes the MVC measurements were repeated. In 2 subjects the procedure was carried out for 1DI first.

6.3.6 Analysis

The MVC sweeps at the beginning and end of the experiment were averaged and compared. They were usually close in value, however in instances when there was a discrepancy the higher of the two values was taken as the maximum. For the first experiment the mean background EMG from the "no stimulation" sweeps and the amplitudes and onset latencies of responses for each "stimulation" sweep were digitised and exported to a spreadsheet to be averaged. Then the actual % MVC for each attempted contraction level, and corresponding mean response amplitudes were calculated.

Since it was the contribution of cortical input to the voluntary activation of the muscle that was of interest, the responses were normalised by relating them to the MVC of the muscle; i.e. $\frac{\text{response peak amplitude} - \text{background EMG}}{\text{MVC}}\%$. The patients' mean response amplitudes were expressed as a proportion of the MVC for the same side muscle, e.g. for right affected deltoid: $\frac{\text{mean amplitude} - \text{mean background EMG}}{\text{MVC right deltoid}}$

Differences between muscles were tested statistically for significance with paired T-tests. One-way ANOVA for related design experiments would also have been appropriate for testing the significance of differences between the three muscles, but this tool lacks the facility for revealing which of the three muscles is different.

6.3.7 Motor Unit Experiment Analysis.

For each subject averages of the surface EMG from 1DI and deltoid were made so as to determine the onset and duration of the short latency response to TMS. All motor unit discharges within the duration of this surface EMG response were included in the analysis.

Each sweep was inspected for discharge of SMU#1, and then for discharge of

SMU#2 or any other motor units. For each intensity used the probability of discharge of SMU#1 and for additional units was then calculated. Sweeps containing "doublets" (SMU firing twice within a very short interval $\sim 4\text{-}7$ ms) were discounted. Mean background firing probability of the motor unit(s) was determined from the 50 control sweeps of data collected before and after the stimulating periods. The motor unit firing probability was considered to be facilitated by the stimulus intensity if the total probability exceeded the spontaneous SMU firing probability.

6.4 Results Experiment 1: Surface EMG responses with voluntary activation in 1DI, biceps and deltoid.

6.4.1 Thresholds.

Even though the coil was positioned in the best place to obtain a response from the gently contracting deltoid, threshold intensities needed to obtain EMG responses in 1DI, when at rest and when active, were still lower. The mean passive and active thresholds for 1DI were 28% and 23% (max. output), thresholds for biceps and deltoid were higher at 37% in both when at rest, and 26% for biceps and 28% for deltoid during gentle contraction. There was also a much greater difference between passive and active thresholds for deltoid and biceps than for 1DI (see table 6.1 for thresholds in all subjects). The difference for 1DI was 5% (max stimulator output), while biceps and deltoid had mean threshold differences of 9% and 11% respectively.

Table 6.1 Threshold intensities with coil in best spot for deltoid (% max. output).

subject	passive thresholds			active thresholds		
	1DI	biceps	deltoid	1DI	biceps	deltoid
1	30	31	27	25	21	24
2	18	22	29	16	19	21
3	31	45	42	26	33	38
4	25	42	37	21	27	27
5	27	34	37	25	28	28
6	29	46	40	26	31	29
7	32	40	40	24	32	30
8	28	38	36	25	30	29
9	26	41	42	22	24	28
10	33	42	46	28	26	30
11	26	31	35	15	23	25
12	31	33	38	28	22	27
mean	28	37	37	23	26	28
S.D.	4.1	7.1	5.1	4.1	5.1	4.1
t		5.6	7.1		2.2	4.1

Max. output of stimulator = 2 Tesla.

1DI thresholds significantly lower; $p < 0.05$

t values are from comparisons with 1DI

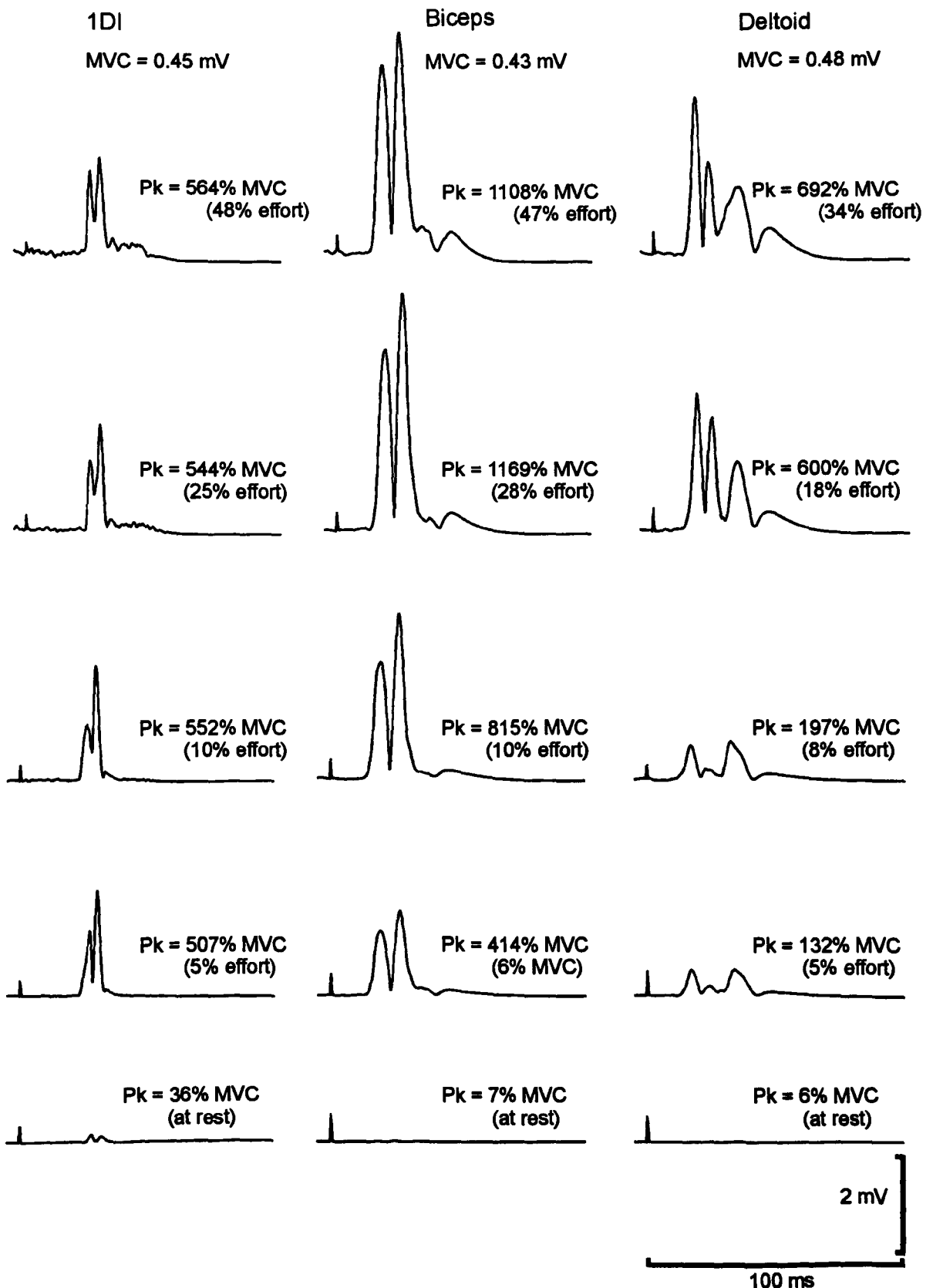


Figure 6.1 Responses to TMS with different levels of voluntary muscle contraction.

Averaged responses ($n=20$) in 1DI, biceps and deltoid, from subject 3. TMS was delivered at 3% max. output of stimulator above the passive threshold for 1DI and deltoid and at threshold for biceps. Response amplitude normalised to baseline EMG and expressed as a percentage of MVC are given (Pk). The voluntary activation of each muscle expressed as percentage of MVC is given in brackets (effort). Note the greatest increase in response amplitude for 1DI occurs between rest and 5% MVC, whereas the increase in response amplitude with effort is more gradual for biceps and deltoid.

6.4.2 Increase in response amplitude with voluntary contraction.

Response amplitudes were larger with increasing voluntary effort in all three muscles in all subjects. Figure 6.1 shows an example from a single subject. The average of twenty EMG responses with five levels of background voluntary contraction are drawn. The increases in amplitude expressed in its normalised form, (i.e. relative to the MVC) are indicated.

Within subjects the maximum normalised responses amplitudes occurred with the largest voluntary facilitation in all three muscles in 33 cases out of 36 (36 = 12 subjects X 3 muscles; see table 6.2). One exceptional case was seen for each muscle and each were from different subjects. It is important to realise that the amplitudes are represented by large values in table 6.2, because single peak values (for TMS response) were compared against a mean of many points (for MVC); but this was common to all data and therefore should not invalidate the normalisation procedure. Mean amplitudes were around 6 times the MVC for 1DI and deltoid and significantly higher, at almost 9 times MVC, for biceps ($t = 3.09$ biceps vs 1DI, $t = 2.92$ biceps vs deltoid, one tailed tests, $p < 0.05$). This may have been as a result of the greater percentage of MVC achieved for biceps than for the other muscles.

Unfortunately although all subjects had attempted to contract to the same relative strengths, (5, 10, 20 and 50% MVC), their actual efforts varied so that mean peak amplitudes calculated for each level of contraction, were not directly comparable across muscles or subjects. To resolve this the data was fitted to an exponential curve:

$$y = b (1 - e^{-ax})$$

("y" refers to the expected amplitude expressed in its new normalised form, "b" is the asymptote, "a" is the rate and "x" is the background level of contraction (%MVC(EMG)).

Table 6.2 Largest normalised response amplitude and %MVC at which it was achieved for each muscle.

subject	1DI		biceps		deltoid	
	% MVC	amplitude**	% MVC	amplitude**	% MVC	amplitude**
1	39	746	28	737	29	553
2	48	548	38	632	35	681
3	48	564	*28	1169	34	692
4	35	826	51	1425	55	995
5	40	498	55	574	45	442
6	53	426	44	892	32	494
7	41	609	56	1027	58	927
8	32	742	59	1462	52	669
9	47	649	38	824	42	596
10	35	495	38	686	*23	291
11	47	772	58	726	61	966
12	*14	683	53	524	30	542
mean	40	630	46	890	41	654
SEM	3	37	3	92	4	63

MVCs (mV)			
	1DI	biceps	deltoid
mean	0.64	0.35	0.57
S.D.	0.19	0.19	0.18

*These efforts were less than the maximum contractions tested with TMS.

**(Peak response amplitude-background)/MVCx100%

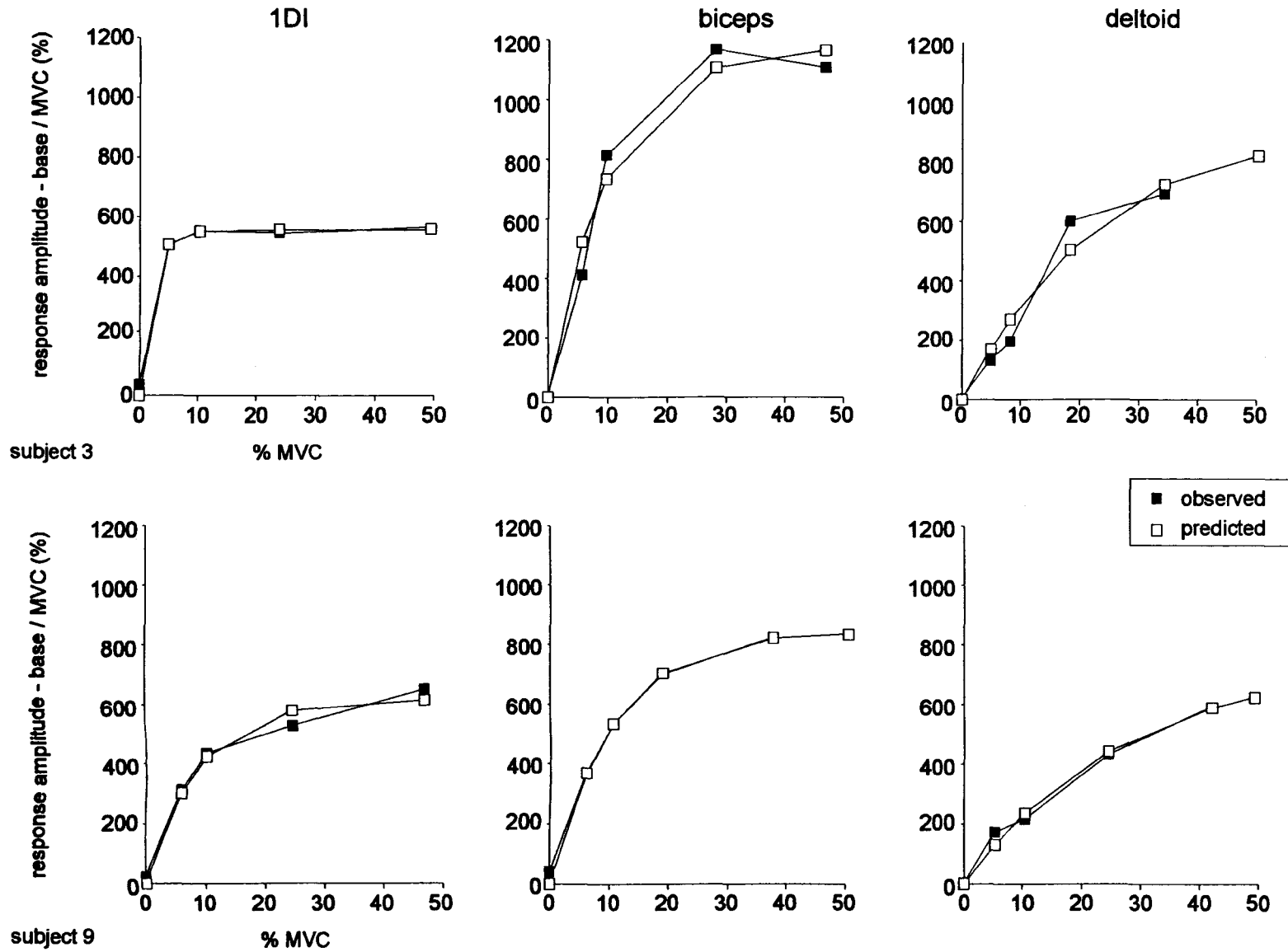


Figure 6.2 Observed and predicted response amplitudes as a function of background level of contraction. Response amplitudes from 1DI, biceps and deltoid in two subjects. Observed data points were derived from the mean of 20 responses. Where predicted values match the observed response amplitudes perfectly, only the open boxes are drawn.

With the data treated in this way the response amplitudes could be plotted as a function of the background level of contraction and comparisons across muscles could be made for each subject. As an illustration of the fitted curves figure 6.2 shows the observed and predicted response amplitudes plotted as a function of voluntary effort for two subjects; the raw data for one of them (subject 3) is presented in figure 6.1.

In all subjects and all muscles the data fitted this expression well. F ratio tests comparing the variances in the observed normalised response amplitudes and the residuals from the predicted values at each level of effort tested yielded high and significant F values. Table 6.3 lists the rate of rise of response amplitudes and the predicted normalised response amplitude at 100% MVC from the curves for each subject and muscle. The predicted response amplitudes varied greatly across subjects (range 330-1723 % MVC), but statistical analysis revealed that maximum amplitudes predicted for 1DI were significantly smaller than for proximal muscles.

It was evident from visual inspection of the individual's fitted curves that there were clear differences between the three muscles in the rate of increase in response amplitude that accompanied voluntary effort. The curves plotted in figure 6.2 show the trend that was typical of the group. 1DI response amplitudes incremented sharply and saturated to a maximum at relatively low levels of background contraction (around 15% MVC). Response amplitudes for deltoid and biceps rose more gradually and did not saturate until higher background contraction levels were achieved. For the two subjects shown saturation occurred with around 30% MVC for biceps and more than 40% MVC for deltoid.

The mean rate of increase in amplitude was significantly larger for 1DI than for biceps, ($t=2.68$, $p<0.05$), which was in turn significantly larger for deltoid ($t=3.64$, $p<0.05$)(see table 6.3). One subject (subject 6) had remarkably low rate values for her 1DI and deltoid curves (i.e. lower than mean + 1 s.d.). However the rate of rise in response

amplitude remained less for deltoid than for 1DI. Another subject (subject 2) had a low rate value for biceps.

The rates given in table 6.3 are derived from the curve fitting process applied to the data. This process assumes that the response amplitude would saturate and this gives rather artificial values (e.g. for subject 6, deltoid). A more meaningful illustration of the differences across muscles is to examine the proportion of the predicted maximum response achieved with different amounts of voluntary effort. Figure 6.3 shows results pooled from all subjects; the proportion of the maximum response predicted from the curve fitting at 5%, 10%, 20% and 50% MVC. From visual inspection of the curves (e.g. see figure 6.2) it was seen that 75% of the asymptote is close to the saturation in growth of the response amplitudes. This is because the rise in the curves become very much shallower as the plateau was approached. Therefore to make clear the greater facilitation of 1DI with lower levels of voluntary contraction than biceps and deltoid, the dotted line indicates the 75% of maximum predicted amplitudes.

6.4.3 Latencies.

It has been observed previously that onset latencies are around 3 ms shorter in active than in resting muscles (Hess, Mills and Murray 1987, Kischka et al., 1993). We found different latency shifts for different muscles. The latency differences between resting and actively contracting muscles were significantly shorter for 1DI than for the proximal muscles (i.e. mean differences were 1.5 ms for 1DI, 3 ms for biceps and 5.4 ms for deltoid. $t = 4.6$ 1DI compared with biceps, $t = 3.0$ 1DI compared with deltoid; $p < 0.05$). No further reduction in latency was observed with contractions over 5% MVC. The mean latencies listed in table 6.4 were compiled from tests in which subjects achieved within 5% of the desired level of MVC.

Table 6.3
Rate of slope relating response amplitude to level of contraction
and response amplitude predicted at 100%MVC, expressed as %MVC.

subject	1DI		biceps		deltoid	
	rate	amplitude	rate	amplitude	rate	amplitude
1	0.350	620	0.140	733	0.020	1094
2	0.120	539	0.005	1449	0.030	1058
3	0.510	554	0.100	1176	0.040	958
4	0.400	727	0.030	1723	0.010	1632
5	0.220	446	0.030	675	0.040	544
6	0.010	666	0.050	1005	0.001	1444
7	0.140	533	0.050	1080	0.020	1162
8	0.040	917	0.050	1500	0.010	933
9	0.110	616	0.090	847	0.030	741
10	0.060	536	0.180	659	0.070	330
11	0.080	801	0.040	800	0.010	1345
12	0.280	633	0.050	578	0.060	658
mean	0.193	632	0.068	1019	0.028	991
S.D.	0.159	131	0.051	374	0.021	381

Predicted amplitude is significantly smaller for 1DI, $p<0.05$, than for biceps or deltoid.

Table 6.4 Response latencies (ms) with voluntary activation.

%MVC	1DI		biceps		deltoid	
	mean	SEM	mean	SEM	mean	SEM
relaxed	22.52	0.43	14.28	0.28	15.42	1.18
5%	21.10	0.39	11.22	0.29	10.10	0.27
10%	20.97	0.36	11.24	0.31	10.04	0.23
20%	21.40	0.45	10.71	0.43	10.05	0.39
50%	21.22	0.39	11.31	0.52	9.79	0.21

Significant differences between relaxed and active values, $p<0.05$

1DI	t = 6.3	biceps	t = 7.9	deltoid	t = 4.4
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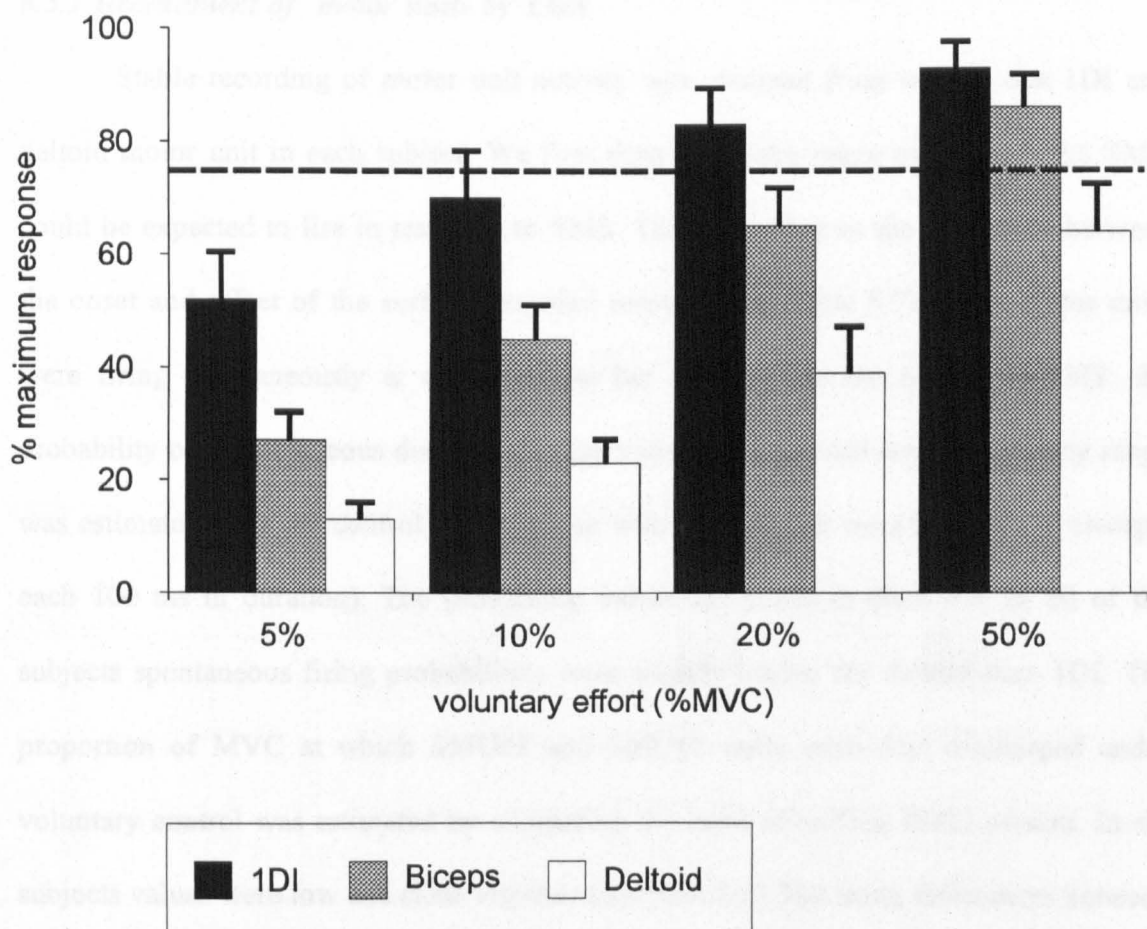


Figure 6.3 The proportion of the maximum response amplitude predicted with increases in voluntary effort.

Results from all subjects pooled. From visual inspection of the curves (e.g. see figure 6.2) it was seen that 75% of the asymptote is close to the saturation of the response amplitudes. This is because the rise in the curves become very much shallower as the plateaus are approached. Therefore to make clear the greater facilitation of 1DI with lower levels of voluntary contraction than biceps and deltoid, the dashed line indicates 75% of the maximum predicted amplitudes.

6.5 Results Experiment 2: Effect of stimulus intensity on motor unit discharge in deltoid and 1DI.

6.5.1 Recruitment of motor units by TMS

Stable recording of motor unit activity was obtained from at least one 1DI and deltoid motor unit in each subject. We first determined the range over which the SMU could be expected to fire in response to TMS. This was taken as the difference between the onset and offset of the surface recorded response (see table 6.7). Since motor units were firing spontaneously at a steady rate but unrelated to the timing of TMS, the probability of a spontaneous discharge falling within the expected response latency range was estimated from the control data taken in which no stimuli were applied (50 sweeps, each 100 ms in duration). The probability values are given in table 6.5. In all of the subjects spontaneous firing probabilities were slightly higher for deltoid than 1DI. The proportion of MVC at which SMU#1 and SMU#2 units were first discharged under voluntary control was estimated by comparing the level of surface EMG present. In six subjects values were low and close together (see table 6.6) The mean differences between SMU#1 and SMU#2 were within 1% MVC for both muscles. In one subject (14) the difference in %MVC between units was greater in 1DI. It can be concluded therefore that the two populations of SMUs tested were very similar in terms of their voluntary recruitment thresholds. The values were not possible to establish for subject 1, since in his test offset in the surface EMG recordings confounded the mean of the rectified data.

Mean latencies of SMU responses ranged from 26.3 ms to 30.8 ms obtained in 1DI and from 14.1 ms to 27.8 ms in deltoid (table 6.7). The 1DI ranges correspond with short latency peaks reported previously that have been presumed to reflect the multiple CS volleys produced by TMS (Hess and Mills, 1986; Day et al, 1989; Boniface, Mills and Schubert, 1991; Palmer and Ashby, 1992). Responses in deltoid motor units with latencies below 20 ms, could be accepted as short latency (Palmer and Ashby, 1992).

Table 6.5 Probability of spontaneous motor unit discharge*.

subject	1DI		deltoid	
	SMU#1	SMU#2	SMU#1	SMU#2
1	0.07	0.07	0.11	0.16
2	0.07	0.08	0.09	0.12
4	0.10	0.11	0.18	0.21
13	0.08	0.09	0.14	0.17
14	0.12	0.21	0.18	0.23
15	0.09	0.10	0.17	0.19
16	0.11	0.12	0.15	0.20

* These values represent the probability of a spontaneous discharge of the motor unit firing within the time that SMU responses were expected in surface EMG recordings.

Table 6.6 % MVC during SMU#1 and SMU#2 tonic discharge.

subject	1DI			deltoid		
	SMU#1	SMU#2	difference	SMU#1	SMU#2	difference
2	2.2	2.9	0.7	1.8	2.8	1.0
4	0.9	1.0	0.1	1.5	1.9	0.4
13	0.5	0.6	0.1	1.0	2.0	1.0
14	0.8	2.0	1.2	0.5	0.9	0.4
15	0.9	1.5	0.5	0.7	2.1	1.5
16	1.9	2.7	0.7	0.5	1.2	0.8

mean	0.55	0.84
S.D.	0.43	0.42

Table 6.7 Latencies of SMU#1s facilitated by TMS (ms)

subject	1DI			deltoid		
	mean	S.D.	accepted range	mean	S.D.	accepted range
1	26.3	1.7	20-30	14.1	2.0	9-20
2	30.8	3.1	20-35	17.7	2.7	10-25
4	28.2	1.8	24-39	22.4	2.2	11-33
13	28.5	2.0	20-35	18.7	1.2	10-32
14	29.6	1.4	24-40	27.8	5.8	15-37
15	27.4	1.5	22-36	19.7	2.3	12-32
16	27.5	1.7	21-32	20.8	3.0	10-30

Four subjects had mean discharge latencies of less than 20 ms. The remaining three subjects' mean discharge latencies for deltoid SMU#1s were equivalent to the medium latency responses observed in proximal muscles by Colebatch et al., (1990).

There were few occurrences of either 1DI or deltoid SMU discharges that coincided with the onset of the surface EMG response. Most of the motor unit discharges occurred well before the end of the surface EMG response. In contrast to previous reports (Hess and Mills, 1986; Day et al, 1989) the discharge latencies of SMU#1 did not appear to decrease as the intensity of TMS was raised. As an illustration the distribution of motor unit discharges evoked by TMS for SMU#1 in subject 1 are given in figure 6.4. This subject's 1DI SMU#1 discharged most often at 25 ms, his deltoid SMU at 15 ms, neither SMUs discharges varied according to stimulus intensity.

Figure 6.5 illustrates in a single subject surface EMG responses (A), SMU responses to TMS (B and C) and SMU discharge during voluntary activation without TMS (D and E). The first unit (SMU#1) to be evoked by TMS was the same unit that was first recruited voluntarily (compare B and D). As the intensity of the TMS was increased a second motor unit (SMU#2) appeared in the response (C). The same unit was recruited voluntarily with increased effort (E).

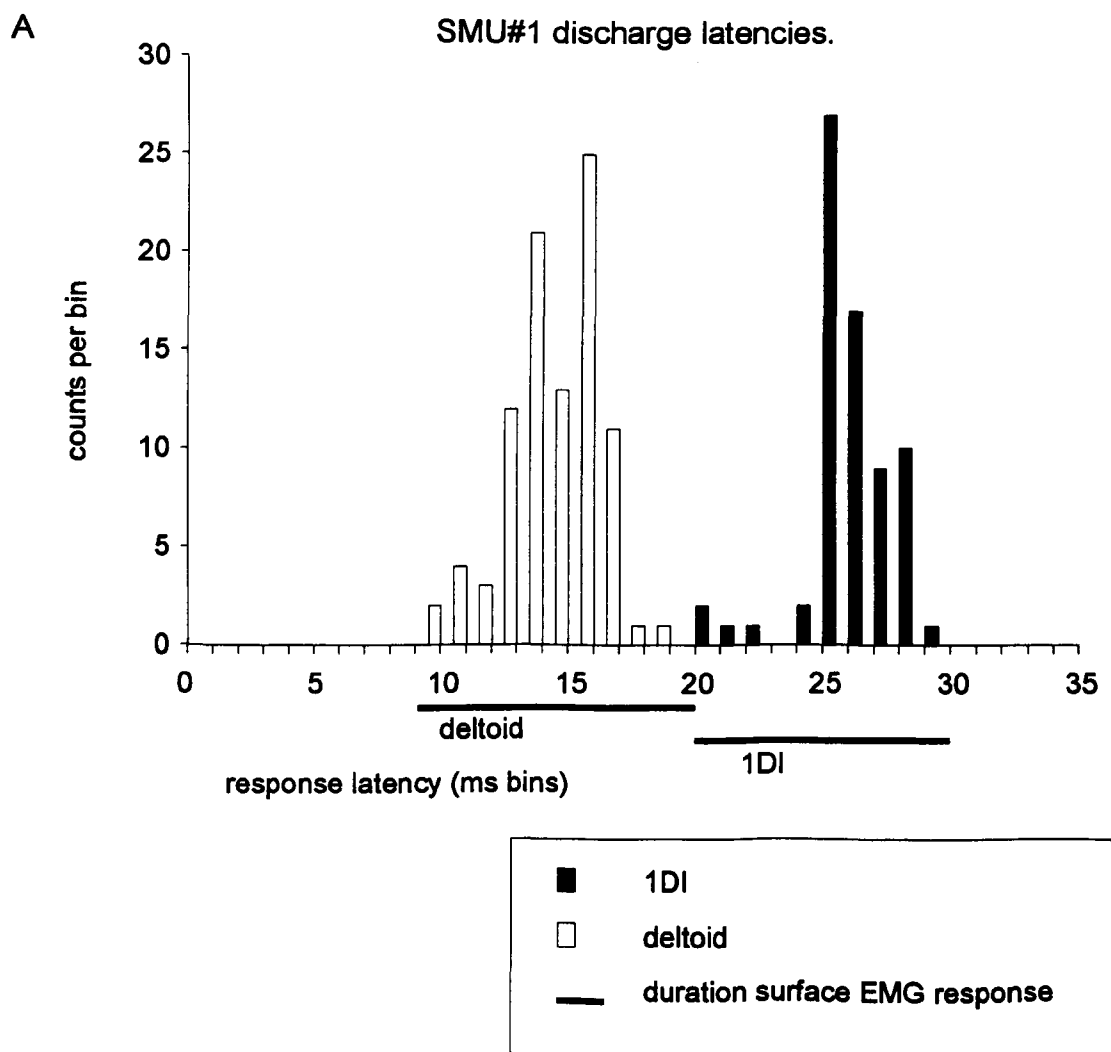
In five of the seven subjects 1DI SMU#1s were recruited at a lower stimulus strength than deltoid SMU#1s (see table 6.8). There were clear and significant differences between 1DI and deltoid in the level of TMS intensity relative to threshold stimulus strength needed to recruit an additional motor unit. Discharge of SMU#2 at a probability level equal to, or exceeding the firing probability, that would have occurred with their voluntary activation, were closer to the threshold intensity for a response in SMU#1 in 1DI than deltoid, for all seven subjects (see figure 6.6). This finding corresponds to the differences found between threshold intensities needed to obtain surface EMG responses from the two muscles when at rest and when contracting gently. The difference between

passive and active thresholds in this experiment and in experiment 1 were less for 1DI (see table 6.1 and 6.8).

6.5.2 Changes in probability of SMU#1 and SMU#2 with stimulus intensity.

As well as affecting recruitment of additional units, increasing stimulus intensity also raised firing probabilities. Since the TMS was not synchronised with the subject's voluntary discharge of the SMU, it is likely that sometimes the unit would fire just before the stimulus and therefore be refractory and unable to respond in some sweeps (Boniface, Mills and Schubert, 1991; Olivier, Bawa and Lemon, 1995). For this reason and also because doublets were excluded from the analysis it was unlikely for P to equal 1, although in subject 14 this was achieved in deltoid SMU#2.

The response probability for SMU#1s and SMU#2 (and/or others) plotted as a function of stimulus strength for three subjects are shown in figure 6.7. There were no differences between the maximum discharge probabilities between muscles, although these had not reached saturation. However, the increase in intensity of TMS needed to increase discharge probabilities of SMU#1 from 0.2 to maximum discharge probability was significantly greater in deltoid (means, n=7: 1DI 0.07 Tesla, deltoid 0.11 Tesla; $t=2.6$, $p<0.05$).



B Mean (S.D.) SMU#1 discharge latency with intensity TMS.

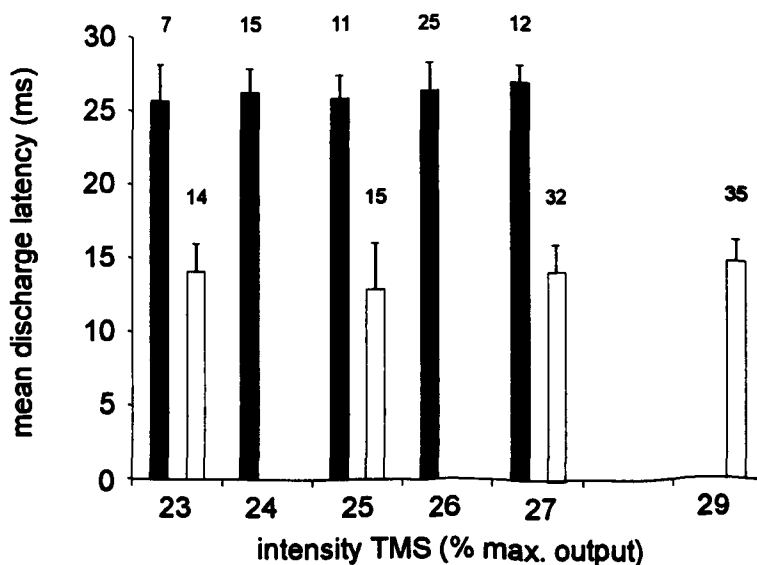


Figure 6.4

A: SMU#1 discharge latencies over the range of intensities, i.e. 40 stimuli at 23, 24, 25, 26 and 27% (stimulator output) during 1DI recording and 23, 25, 27 and 29% during deltoid recording.

B: Mean SMU#1 discharge latency with intensity TMS (S.D. shown by error bars). The numbers over each bar refer to the total number of SMU#1 discharges at each intensity.

Activation by TMS

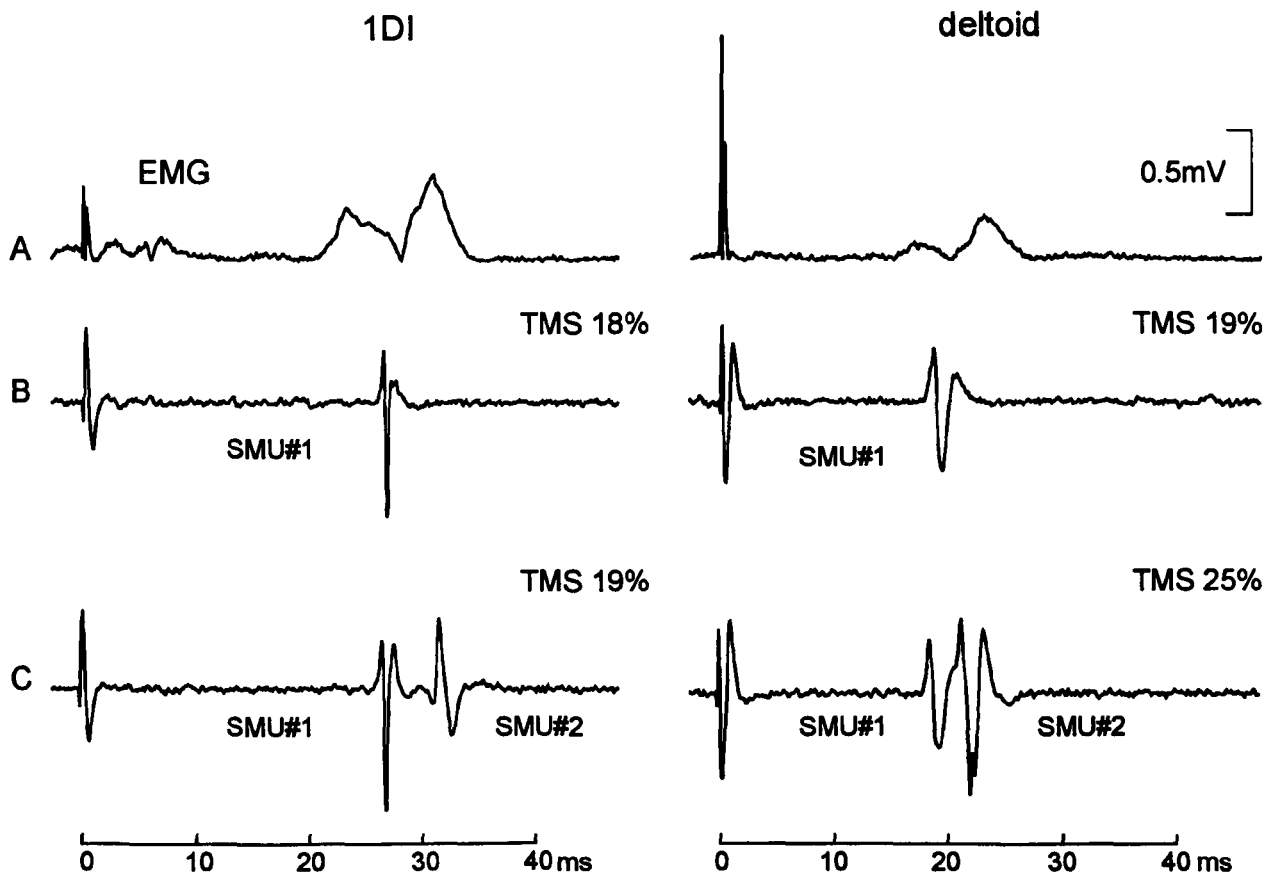


Figure 6.5 SMU discharge in 1DI and deltoid with TMS and voluntary activation.

Single sweeps from subject 15 are shown.

A Surface EMG responses.

B SMU responses to TMS at low intensity.

C SMU responses to TMS with increased intensity.

D SMU recruited first with voluntary activation.

E SMUs recruited with increased voluntary effort.

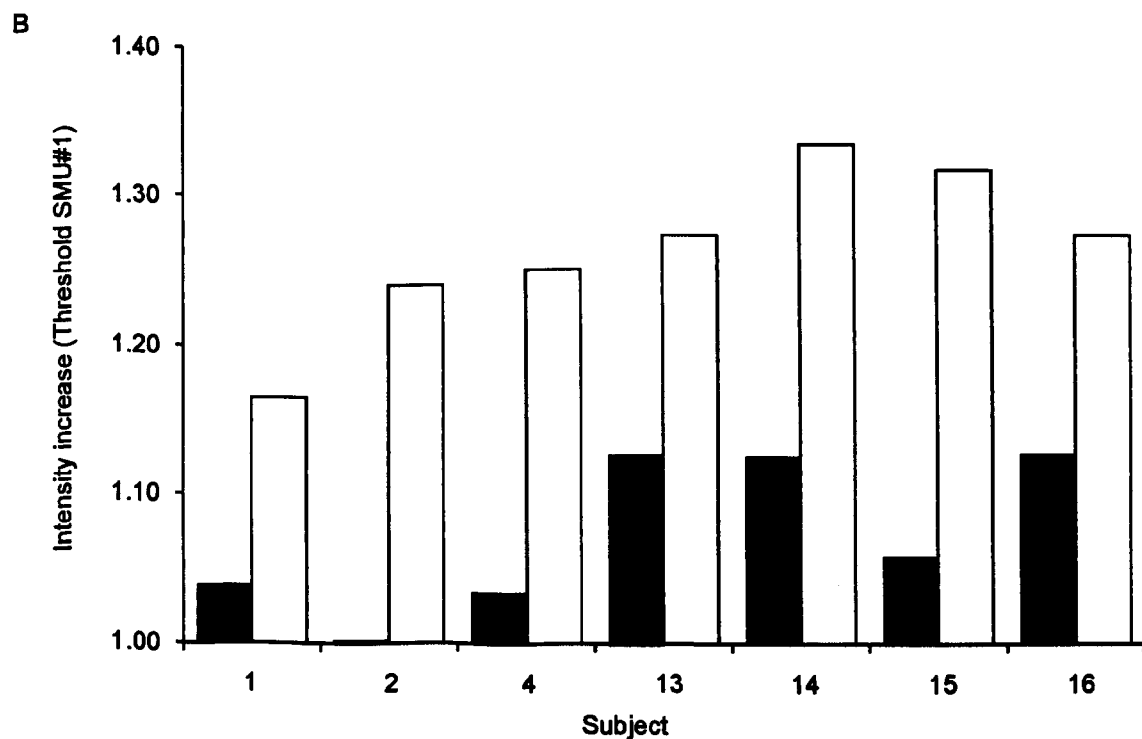
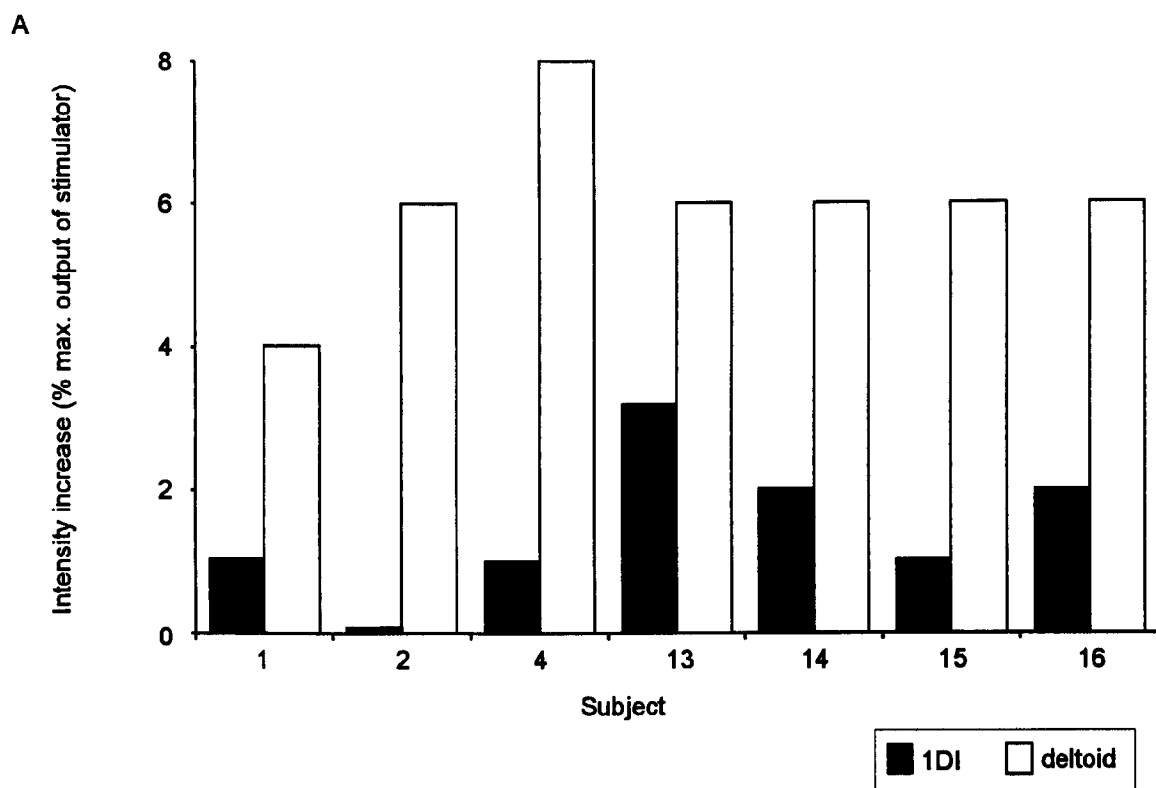


Figure 6.6 Increase in TMS intensity required to recruit additional motor units.

A: expressed as % maximum output of stimulator.

B: expressed as multiple of threshold for SMU#1.

Threshold = The lowest TMS intensity required to discharge SMU at a probability greater than that of the unit's discharge during voluntary activation in the absence of stimulation.

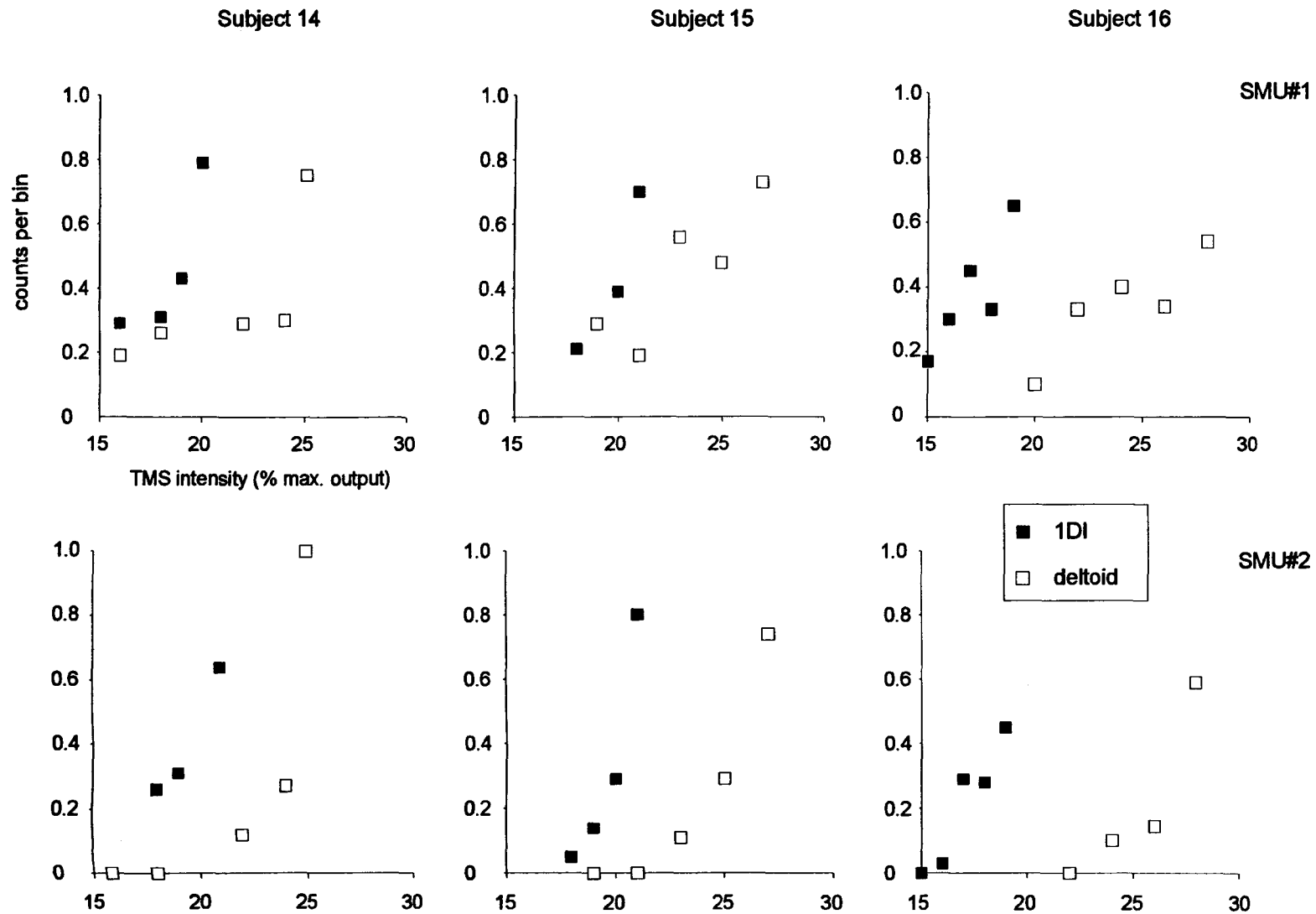


Figure 6.7 Probability of discharge for SMU#1 and SMU#2 with strength of TMS.

Table 6.8 Threshold intensities for SMU#1 and surface EMG responses.

subject	SMU#1	1DI		SMU#1	deltoid	
		T active	T passive		T active	T passive
1	23	24	27	23	22	27
2	18	17	19	25	21	28
4	29	25	27	32	27	37
13	26	24	29	22	25	34
14	16	16	24	18	18	27
15	18	17	19	19	18	21
16	16	16	19	22	18	29

Thresholds expressed as % max. output.

6.6 Experiment 3: Variation in amplitude of deltoid responses with level of voluntary contraction in three stroke patients.

6.6.1 Arm strength and function at time of test.

The three patients (JB, DF and RD) were selected from the more severely affected group of patients (group B) in the main study. All three had suffered complete paralysis of the arm as a result of the stroke and had recovered slowly over the following weeks and months. They had no responses to TMS in deltoid in the early weeks after stroke when they were recruited to the longitudinal study. Table 6.9 summarises their details and improvement in the strength of the affected deltoid. At the time of this investigation, (9 months to 30 months after stroke) all three patients were able to raise the arm, with elbow flexed to approximately 90° of abduction, and to hold it there against strong resistance (i.e. to grade 4 and 5 MRC scale). Deltoid MVCs (EMG) on the affected side were the same as the unaffected side for JB and approximately half the values obtained from the unaffected side for DF and RD. JB was unable to move the arm out of the flexor synergy pattern, but DF and RD were both able to flex the shoulder to 90° and extend the elbow simultaneously to produce a reaching movement. DF was able to use this reaching movement in his daily living because he had also recovered reasonable dexterity. RD's finger movement was poor at the time of this test and so her upper limb function was very limited.

6.6.2 Thresholds.

Responses were obtained from the affected deltoids when active and the threshold stimulus strengths were higher than those of the unaffected side (see table 6.10). Thresholds for resting muscle were not obtainable for the affected side in JB and DF.

Table 6.9 Patients' details

Patient	Age	Lesion (CT report)	MRC strength rating over recovery period				At test (months)
			2 weeks	6 weeks	12 weeks	24 weeks	
JB	59	L cerebral haemorrhage	0	0	0	2*	4 (28)
DF	71	L internal capsule	0	0	2*	3	5 (30)
RD	54	L basal ganglia and paraventricular area	1	2*	4	4	4 (9)

* Contralateral response to TMS first seen in affected deltoid at this test

Table 6.10 Patients' active and passive TMS thresholds (% max. output).

Patient	unaffected deltoid		affected deltoid	
	T active	T passive	T active	T passive
JB	20	24	38	>55
DF	21	35	28	>55
RD	37	40	42	52

Table 6.11 Rates and response amplitudes at equivalent % unaffected MVC

patient	affected deltoid		max. amplitude	unaffected deltoid			
	test TMS intensity	rate		test TMS intensity	rate	amplitude (at % unaffected MVC)	
JB	43%	0.001	219	27%	0.005	698	(50%)
				43%	0.017	790	(50%)
DF	33%	0.09	44	26%	0.014	100	(20%)
RD	45%	0.023	492	42%	0.001	490	(30%)

Note: Mean - 2 S.D. normalised response amplitude in right deltoid of normal subjects
at 10% MVC = 116
at 30% MVC = 293

6.6.3 Response amplitudes related to voluntary activity.

Because the patients actual efforts varied from their target contractions (5, 10, 20 and 50% MVC), the mean peak amplitudes were fitted to the exponential curve that was used for the normal subjects data in experiment 1; $y = b (1 - e^{-ax})$. Fitted response amplitudes have been plotted against the unaffected side % MVC in figures 6.8-10. The rate of increase in response amplitudes and the maximum amplitudes on the affected side, together with equivalent values for the unaffected side are summarised in table 6.11.

JB achieved the same MVC and almost the same contraction levels for both deltoids up to 50% MVC during the test, yet his mean response amplitude at 50% MVC from his affected deltoid was less than a third of that recorded from the unaffected side at 27% and at the same strength (43%). It was also lower than the response amplitudes at 30% MVC for right deltoid in the normal subjects.

DF's voluntary contractions were weaker on the affected side than the unaffected side. His maximum response amplitude on the affected side (normalised to the side MVC) was less than half the amplitude achieved at equivalent activity on the unaffected side (i.e. 20% of the unaffected MVC). In addition, the rise in predicted response amplitudes appeared to have saturated at low force. Hence the greater value for the rate of increase in response amplitude on DF's affected side. The largest of DF's responses on his affected side, and also his responses on the unaffected side at 20% MVC, were lower than any of the normal subjects' responses at 10% MVC.

RD's results were different (see figure 6.10). Her response amplitudes from the affected and unaffected deltoid were very similar. The mean maximum response achieved by her affected deltoid equalled the responses from the unaffected deltoid and fell within the range of response amplitudes recorded from normal subjects at the equivalent 30% unaffected MVC. The responses at lower contraction levels were even a little larger on the affected side, making the rate value higher than the unaffected side.

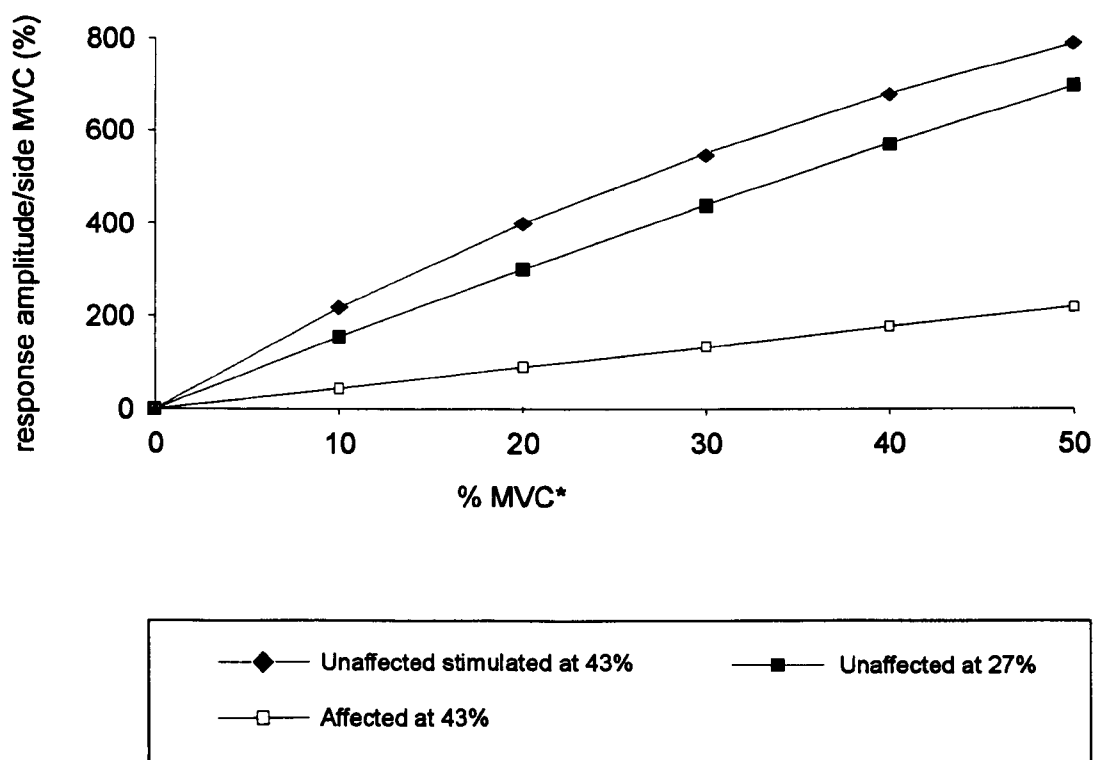
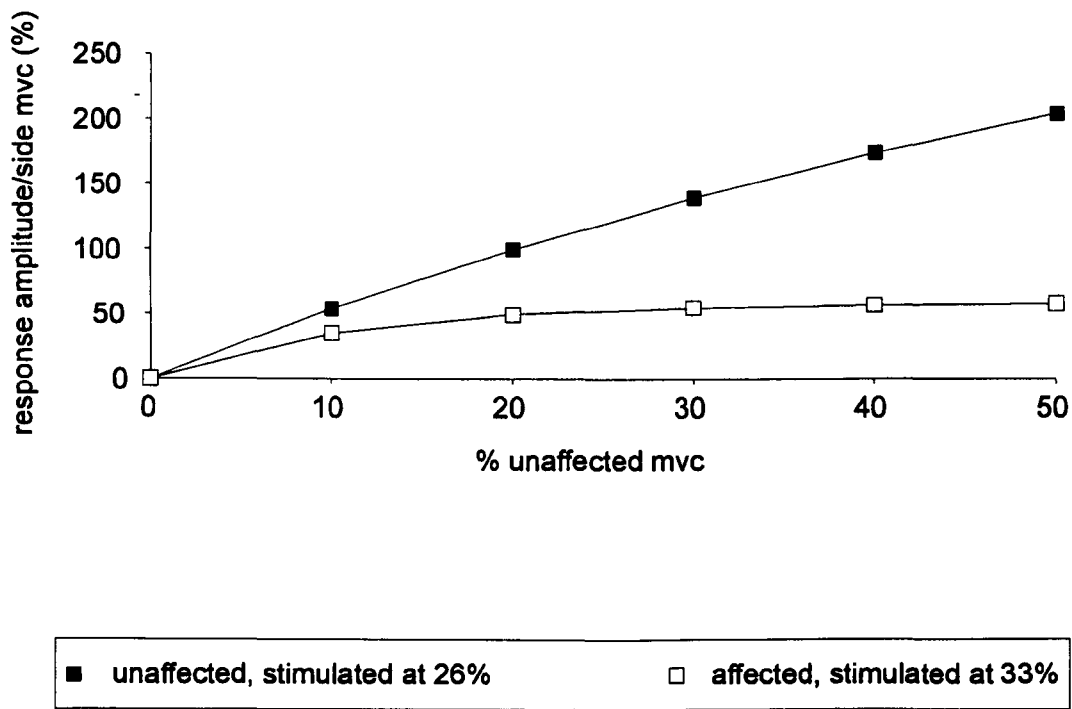


Figure 6.8 Patient JB: Facilitation of responses in affected and unaffected deltoid by voluntary contraction.

Response amplitudes predicted from fitting mean normalised amplitudes to the exponential curve that was used for the normal subjects data and plotted against unaffected side % MVC.
 *This patient's affected side MVC was the same as his MVC on the unaffected side.

A. Predicted response amplitudes



B. Response amplitudes fitted over range of voluntary contraction tested.

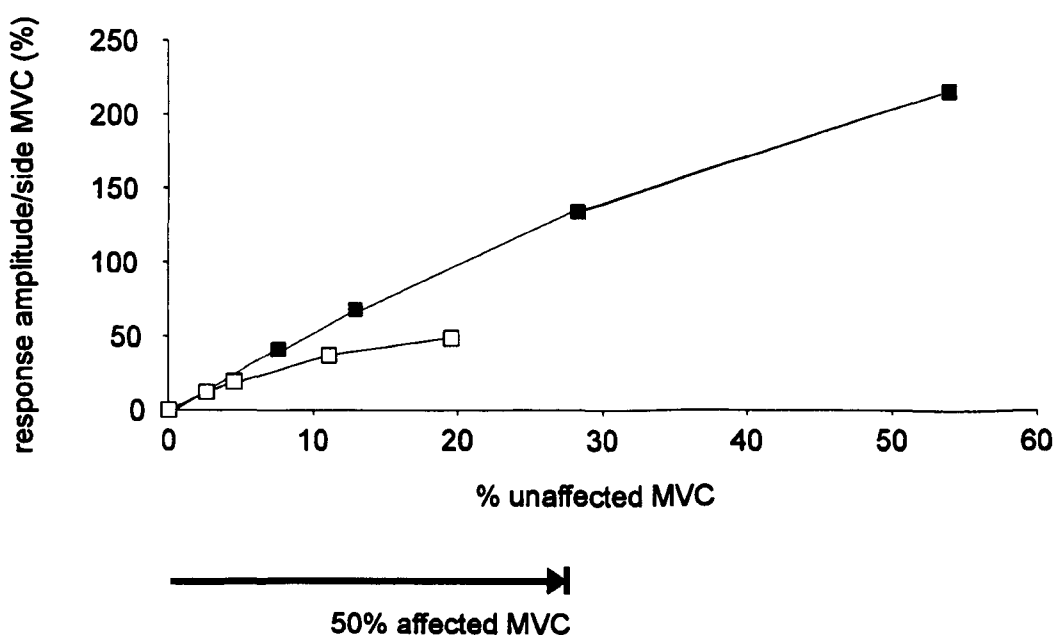
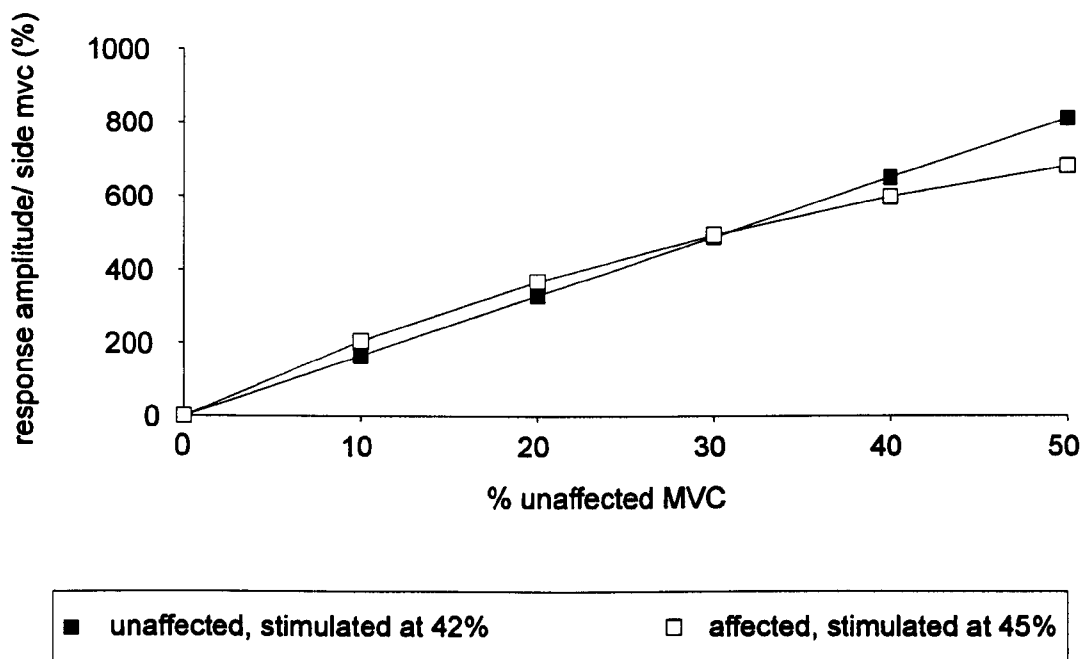


Figure 6.9 Patient DF: Facilitation of responses in affected and unaffected deltoid by voluntary contraction.

A. Predicted response amplitudes



B. Response amplitudes fitted over range of voluntary contraction tested.

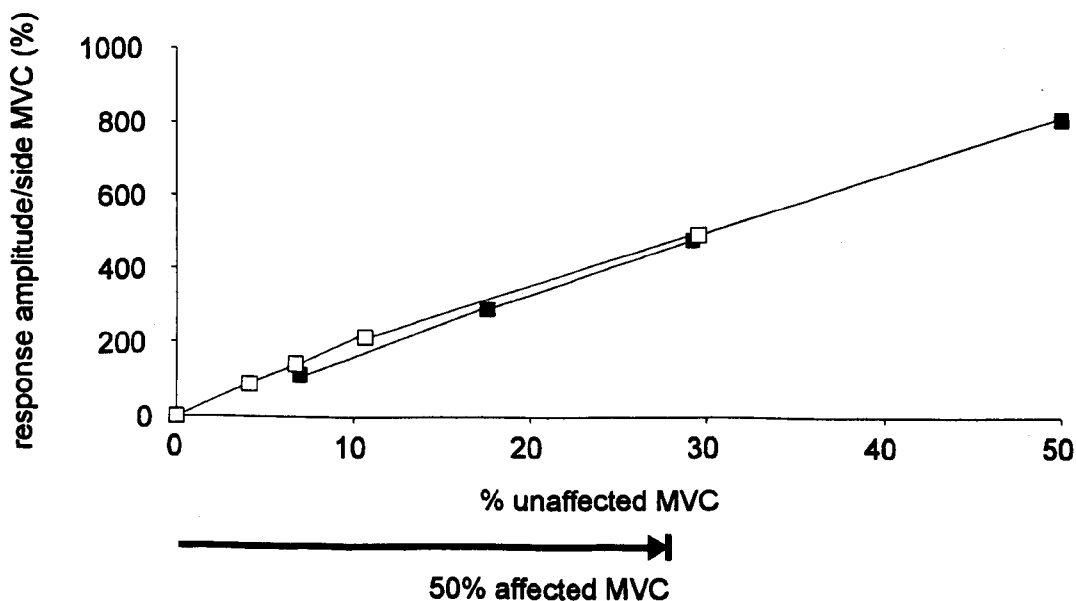


Figure 6.10 Patient RD: Facilitation of responses in affected and unaffected deltoid by voluntary contraction.

6.7 Discussion

6.7.1 Facilitation of EMG responses to TMS with voluntary activation in proximal and distal muscles.

Response amplitudes to TMS are increased by voluntary activity but this facilitation is different in proximal and distal muscles. In the first experiment, 1DI response amplitudes were found to increment sharply and saturate at low contraction levels. In contrast responses in deltoid rose more gradually and did not plateau until much larger efforts were generated. Biceps rate of increase lay between 1DI and deltoid.

These results confirm those obtained by Kischka et al. (1993) showing that biceps' gradual increase of response amplitude with voluntary effort differed from the abruptly incrementing response amplitudes seen in an intrinsic hand muscle, abductor digiti minimi, (cf. Hess, Mills and Murray 1987). In the analysis of Kischka et al. (1993), the average of only three or four responses at levels of contraction 0%, 10% and 20% or 25%, 40% and 60% maximum force from 36 subjects were pooled. Since there is considerable variation in response amplitude particularly at low levels of background contraction, the results from my study in which from 40 stimuli were delivered at each of five different levels of voluntary activity bring greater confidence to the differences between muscles in the relationship between response amplitude and level of activity.

6.7.2 Corticospinal influences on voluntary contraction of different muscles.

EMG responses to TMS are the product of all inputs to the motoneurones. I set out to consider how important the CS input was for voluntary activation of distal and proximal muscles. Kischka et al. (1993) have suggested that the more linear response increase with voluntary activation of biceps can be explained satisfactorily as being due to facilitation by spinal facilitatory mechanisms. A number of investigations have shown that spinal reflex responses increase in proportion to the level of activity within the motoneurone pool. For example it has been shown that short latency EMG responses in

thumb and wrist flexors following perturbation and in elbow flexors and extensors following vibration increase linearly with background voluntary EMG (Marsden, Rothwell and Day 1983, Bedingham and Tatton, 1984, Matthews 1986). A similar relationship has been found for long latency reflex responses of presumed transcortical origin in flexor pollicis longus with background voluntary contraction at low force levels (Marsden, Merton and Morton 1972, 1976; Marsden, Rothwell and Day 1983). This has become known as the "automatic compensation of reflex gain" principle.

Before comparing the relationship of the amplitude of responses to TMS to voluntary effort between muscles, it is important to consider the range of activity in which comparisons may be safely made. Variation in rate of rise of response amplitude in proximal and distal muscles may be affected by differences in the size of motoneurone pools and the resulting mode of force production for each muscle. 1DI, deltoid and biceps are comparable because they have a similar distribution of fibre types, with approximately half of their fibres being type I: belonging to slow twitch oxidative motor units (Johnson, Polgar, Weightman and Appleton, 1973). However, the means of force production over their range of activity differs. The proximal muscles generate force by recruiting new motor units throughout most of their force range, whereas in 1DI forces above 40% of MVC depend on increasing the rate of already active motor units (Milner-Brown et al., 1973; Kukulka and Clamann, 1981; DeLuca et al., 1982). When TMS is triggered at random to the unit's voluntary discharge, the rate of a tonically firing motor unit has little effect on the probability of the unit's response to TMS (Olivier, Bawa and Lemon 1995), but a motor unit can fire more than once within the duration of an EMG response, particularly at high stimulus intensities (Day et al., 1989; Bawa and Lemon 1993). However it is likely that recruitment of inactive units has a greater influence on the amplitude of EMG responses to TMS. Indeed at 40% MVC response amplitudes in 1DI had already saturated.

The responses to TMS seen in 1DI did not increase in a linear fashion up to 40% MVC. In many of the subjects the rate of increase in response amplitude had begun to fall at half that activity level. Larger increases in response amplitude occurred at lower levels of contraction, thus it would be reasonable to conclude that in 1DI many more motoneurons were near to threshold in this low range of activity than in deltoid. The additional CS input excited by TMS, rather than from spinal mechanisms may have been responsible for making them discharge. Similar early saturation is apparent in long latency stretch reflexes. These reflexes which are more prevalent in distal muscles, are probably mediated through the sensorimotor cortex (Matthews, Farmer and Ingram, 1990; Taylor, Fogel, Day and Rothwell 1995) and can compensate for small but not large torque disturbances (Marsden, Rothwell and Day 1983).

Although the automatic compensation of reflex gain principle has been used to compare the response amplitude increases to TMS between muscles, spinal mechanisms cannot be ruled out in explaining the 1DI results of this experiment. A non-linear increase in response amplitudes to TMS may be the result of greater weighting of low threshold units by other inputs (Buller, Garnett and Stephens, 1980; Kernell and Hultborn, 1990).

Since any inequalities in the distribution of afferent inputs were not excluded from the first experiment it is impossible to confirm that the large increases in response amplitude to TMS in 1DI were due to cortical influences. However the motor unit experiment results (discussed below) do provide clear evidence that the CS input activated by TMS is a major determinant of the pattern of response seen in 1DI.

The response amplitudes to TMS in biceps and especially in deltoid did increase in a more linear fashion over the activity range tested, and were predicted to continue to rise with higher levels of background EMG. At least in these muscles the cortical input that can be excited by TMS does not seem to be especially important for producing either high or low levels of voluntary activity.

6.7.3 Large responses are obtained from proximal muscles with substantial voluntary facilitation.

Since the early transcranial electric stimulation and TMS work, in which muscles were tested at rest, it has been accepted that substantially larger response amplitudes are obtained from distal muscles than proximal ones. Rothwell et al. (1987) and Brouwer and Ashby (1990) expressing response amplitudes as a percentage of the maximum M wave obtained larger responses from small hand muscles than from biceps. (Kischka et al. (1993) and Hess Mills and Murray (1987) did not attempt to compare maximum response amplitudes, they chose instead to represent for each contraction level, the proportion of the maximum amplitude achieved for respective muscles). It was therefore somewhat surprising to find that there was no significant difference in the normalised response amplitudes of 1DI and deltoid when contracting at a mean maximum of 40% MVC, and that when fitted to the function, values for maximum response amplitudes predicted that proximal muscle responses would be larger than for 1DI. 1DI and deltoid MVCs' had similar absolute values (millivolts), therefore the results for these muscles at least, cannot have been skewed by the normalisation process.

The explanation may be simply related to the difference in number of motor units being recruited to produce such large efforts. Deltoid has about 1000 units altogether, compared with only 120 in 1DI. Alternatively it is possible that the position of the coil somewhat compromised the size of responses from 1DI since it was positioned in the best place to obtain a response in deltoid. Nevertheless the threshold intensities required to obtain responses in 1DI at this location were still lower than for the other muscles.

6.7.4 The difference in response latency between relaxed and active states is larger in proximal muscles than in 1DI.

In agreement with findings reported by Hess et al, (1987) and Kischka et al. (1993) the latency of responses to TMS was decreased with only very gentle background

contractions. After their investigation of TMS responses in small hand muscles, Hess et al. (1987) suggested the latency jump may have arisen due to the size principle recruitment order of motoneurons. If this was so the responses at low levels of contraction would have involved discharge of small slowly conducting motoneurons and then as more voluntary drive was produced larger and faster conducting motoneurons would deliver an earlier response. However my results agree with those of Kischka et al. (1993): after the generation of gentle contractions, further increases in voluntary background contraction produced little or no reduction in latency. If recruitment order was responsible, further reductions in the latency especially in the rather "recruitment dependent" proximal muscles, would be expected as the background contraction became even stronger.

Kischka et al. (1993) suggested that if TMS response latencies were attributable to the size principle hypothesis, then distal muscles being supplied by longer motor axons, would show a more pronounced reduction in latency with the recruitment of faster units. In fact they found that the latency jump was marginally greater in more proximal muscles than in the hand muscle, abductor digiti minimi. My results have shown a significant difference in the size of the latency shift between muscles. Much larger differences between response latency at rest and in active muscle, were evident in the proximal muscles. The recruitment explanation for latency shift was also disproved by motor unit studies that showed the same units were discharged earlier when TMS was delivered while the muscle was active than when relaxed (Thompson et al., 1991). It is now generally accepted that the longer latency of responses in relaxed muscles are symptomatic of the time taken for temporal summation of multiple descending volleys (i.e. D and I waves, see section 1.7, page 33) at the CM synapse with the motoneuron, although a cortical contribution, also due to temporal summation may also exist (Edgley et al., 1990). If the latency difference is due to the added time required for temporal

summation then it would appear that much more summation is required to discharge proximal muscle units. Some agreement for this was found in the results from the motor unit experiment.

6.7.5 Recruitment of motor units by TMS.

The results from the motor unit experiment indicate that the CS input makes a significantly greater contribution to low levels of activity in 1DI than in deltoid. The subjects in this experiment maintained the same very slight contraction throughout, so as to keep a low threshold motor unit firing at a steady rate, only the stimulus intensity was changed. Thus all inputs to the motoneurons except for that activated by TMS should have been stable. Bawa and Lemon (1993) showed that the CS volley recruits motor units in a progression similar to the rate and recruitment principles governing voluntary activation. Indeed the first units recruited by TMS in my tests were the same units recruited by voluntary contraction and they were recruited in the same order by TMS and voluntary activation.

In all seven subjects smaller increases in stimulus intensity were needed to increase the firing probability of SMU#1 and to recruit additional units in 1DI than in deltoid. This was true for both absolute and relative differences in TMS intensity. These additional units were all low threshold and provided small increases in the surface EMG activity. In the light of results from the first experiment it is important to note that the %MVC increase provided by the recruitment of SMU#2 during voluntary activation was not consistently larger for deltoid; one of the seven subjects had greater increase in 1DI's surface EMG activity. The surface EMG results from experiment 1, showing larger increases in the amplitude of responses at low force levels in 1DI than in proximal muscles, may have been regarded as simply being a reflection of the number of motor units recruited at each level of activity. However, these motor unit recruitment results suggest that the increase in response amplitude to TMS was brought about by greater

influence of CS inputs to the motoneurone pool rather than any differences in number of motoneurones that were discharging or close to discharge at the time of the arrival of the CS volley.

It was interesting that in some subjects responses from the first SMU recruited in deltoid were rather late to be considered as short latency. In view of this it could be argued that a comparison of the two muscles should not be made. But against this is the observation that in previous studies medium and long latency (ca 40 ms) motor unit discharges have been obtained when short latency discharges could not be evoked in proximal muscles (Colebatch et al., 1990; Palmer and Ashby, 1992). The failure to evoke many short latency discharges, even at the higher intensities used, is itself probably symptomatic of the relatively small influence of the CST over deltoid motoneurones; much less input from TMS is required to excite the fast CM component and to subsequently influence motoneurones in 1DI than in deltoid.

6.7.6 Contribution of CS input to voluntary contraction of deltoid in three stroke patients.

In two of the three patients smaller responses to TMS were obtained on the affected than on the unaffected side during the production of equivalent voluntary contractions. These two patients' response amplitudes were also smaller than those obtained from comparable efforts in the normal subjects; although it should be remembered that the normal subjects were tested with stimulus intensities that were higher relative to threshold. If it is assumed that TMS can recruit the CS elements involved in voluntary activation for both affected and unaffected sides, then these patients must have achieved muscle contraction with less than normal CS input to the deltoid motoneurones.

Perhaps the most convincing case for redistribution of inputs to the motoneurones comes from patient JB. He survived a large cerebral haemorrhage and suffered severe cortical damage; both his speech and sensorimotor function were profoundly affected. His

lack of responses and recovery in distal muscles suggested major disruption of the CS tract, yet he eventually achieved an MVC in the middle fibres of his right affected deltoid that was comparable to the unaffected side. The responses to TMS were small throughout the range of his voluntary effort suggesting that there was much less contribution to the motoneurons from CS inputs on the affected side. Presumably over the course of JB's recovery other inputs e.g. from reticulospinal fibres, compensated for the loss of CS inputs.

To a lesser extent DF's small response amplitudes on the affected side also suggest an increased dependence on other inputs in activating deltoid. With respect to MVC of the muscle it seems they were not as "successful", because his affected side MVC recovered to only half that of the unaffected side. He too took many months to regain strength, but the appearance of responses in distal muscles and recovery of hand function indicate that CS inputs to the motoneurone pools were not completely lost. Indeed the superior repertoire of arm movements that he regained may well be due to his ability to make use of the remaining CS fibres.

The last patient's results were different. Her responses were not reduced with voluntary effort, though her MVC was smaller on the affected side. Recovery happened faster; she regained power in the arm within three months of stroke and responses to TMS were present in deltoid at six weeks post stroke. At six months responses were obtained from the hand, though she did not recover hand function until later. Perhaps the degree of disruption in CS fibres that projected to the proximal motoneurons was not severe enough to trigger compensation by other inputs.

6.7.7 Implications of results for obtaining responses in proximal muscles and for recovery after stroke.

The absence of responses to TMS may be due to failure to stimulate CS cells that project to the motoneurons of the muscle, or to failure of the CS volley to bring the

motoneurons to threshold. Although the topographical area over the cortex from which a response may be achieved in deltoid is relatively small in comparison with 1DI (Wassermann, McShane, Hallett and Cohen, 1992), I was careful in these experiments to eliminate the former as a cause, by careful positioning of the coil to get optimum responses from deltoid. Thus the impact of the CS volley on the motoneurone pools could be compared between muscles. Taken together the results of the first two experiments confirm that CS input is more important for controlling voluntary activation at low force levels in distal than it is in proximal muscles in normal subjects.

The greater influence of CS input to excite 1DI motoneurons at low activity levels accounts for the ease in which responses to TMS are obtained in normal subjects. In comparison CS input to motoneurone pools of deltoid and biceps has a rather weaker effect. These motoneurone pools must depend more on inputs from other sources to bring them to discharge. Thus a response may not be obtained in deltoid unless the subject is already activating the muscle.

In some stroke patients who have sustained severe disruption to the CST it seems that voluntary activity in deltoid can be achieved with a diminished CS input. Their recovery therefore must be mediated by increased effectiveness of other descending systems. This mechanism for recovery appears not to be available to distal muscles for which CS inputs are much more important: they are both necessary and may be sufficient for many purposes.

CHAPTER SEVEN.

DISCUSSION

CORTICOSPINAL CONNECTIVITY AND UPPER LIMB FUNCTION AFTER STROKE.

This study was undertaken to investigate the effect of stroke on task-related organisation within the motor cortex and to identify mechanisms that contribute to recovery of arm and hand movement. In this chapter the findings across the investigations are drawn together to consider their merit in improving understanding of stroke and its recovery and any implications for clinical practice.

7.1 The effects of CS loss on task-related organisation within the motor cortex.

Magnetic stimulation studies show that stroke can result in a significant reduction in the number of rapidly-conducting CS neurones with effective CM connections to the motoneurones of their target muscles. If it is assumed that there is considerable redundancy within the "colony" of CS cells projecting to a given muscle, it may be that after stroke, partial recovery of hand function requires the patient to use all of their remaining CS cells to perform all the tasks that involve a particular muscle. They may have lost redundancy in the CS population. Thus it was predicted that stroke patients would not show task-related variation of response amplitudes to TMS. This prediction was verified in stroke patients with clear cut internal capsule lesions, who recovered useful but nevertheless deficient hand function. They did not show the same task related organisation within the cortex as previously reported in normal subjects (Flament et al., 1993). Responses to TMS obtained in 1DI during various isometric grips were not significantly larger than responses that were produced during isometric abduction of the index finger.

However the results were somewhat complicated by the finding that the task-related variation of response amplitudes in normal older subjects differed from that found in the young subjects previously investigated.

The reason for differences in the variation of task-related responses between the young and older normal subjects requires clarification, before the stroke patient data can be adequately interpreted. Investigations testing separately any effects of age and skill are needed. So far to my knowledge there have been no studies reporting effects of age on cortical activation evoked during task performance. Similarly I have not found any reports of the effects of skill practice on response amplitudes *during* performance of different tasks. In looking at task-related variation of response amplitudes my investigations and previous task experiments (Datta et al, 1989; Flament et al., 1993; Schieppati et al., 1996) have been interested in the differential excitability of CM cells across different tasks requiring use of the same muscle and critically during performance of the task. Previous studies of the effects of skill using TMS have concentrated on mapping the area of sensorimotor cortex that represented the digit(s) used in the skill (Pascual-Leone and Torres, 1993; Pascual-Leone et al. 1995). In these investigations TMS was applied to the relaxed subject giving some idea of the relatively stable changes in cortical excitability that outlast the actual performance of the skilled task.

In the absence of a secure interpretation of the results from normal aged-matched subjects, perhaps it is acceptable to use as a control, the pattern of task-dependency of responses to TMS from the patient's unaffected hand. In contrast to the responses from the unaffected hand, responses from the affected side 1DI, in patients who had made a far from complete recovery of their dexterity, did not vary significantly with task, suggesting that the same number of cells were active irrespective of the task being performed. These patients were known to have had little or no upper limb movement immediately after stroke, and most of them took many weeks and months to recover any hand function.

How did this happen? Was their recovery explained by reorganisation of the CST or by increased contribution of another descending system? The results of the longitudinal study of recovery went some way towards answering these questions.

7.2 Reorganisation within the CST is necessary for recovery of hand function.

In the longitudinal study the relationship between recovery of arm and hand function and the presence of short-latency contralateral and ipsilateral EMG responses to TMS in distal and proximal upper limb muscles were examined. In patients who were initially unable to move the affected limb, responses were often absent. In those that later recovered the ability to activate 1DI and EDC, responses returned at or just before this stage of recovery. Subsequent investigations of the facilitation of EMG responses in 1DI and in proximal muscles by voluntary contraction and of the recruitment of low threshold single motor units by increasing the intensity of TMS, confirmed the greater contribution of CS input over the 1DI motoneurone pool. Compared with deltoid response amplitudes in 1DI rose sharply and then saturated when background EMG activity was still very low. Very much smaller increments in the intensity of TMS were needed to recruit additional single motor units in 1DI than in deltoid. With such a powerful influence of CS input, it would be expected that absence of a response in 1DI would signify considerable disruption of the CS system projecting to the muscle, rather than there being insufficient background facilitation within the motoneurone pool to obtain responses.

In the light of these findings it is proposed that patients who have no EMG activity or responses to TMS in distal muscles lack hand function because of the reduction in CS connections and not simply because they cannot use those that remain. It is very likely that patients who recover hand function, do so as a result of strengthening or novel connections made by the CS system. Given the history of some of the patients that were recruited to the task study many months and years after stroke, it seems probable that the

slow recovery of their hand function was also regained through CST reorganisation, rather than only by learning to use the remains of the system that survived stroke.

After complete bilateral lesions of the CST the loss of relatively independent finger movement needed for precision was the sole permanent impairment in monkeys (Lawrence and Kuypers, 1968a). Gross hand movement was only lost after subsequent interruption of the rubrospinal tract (Lawrence and Kuypers, 1968b), and was not abolished in monkeys whose CST had not previously been sectioned. The CST has a much wider influence in man than in monkey. The effects of a lesion to the CST may not be confined to loss of relatively independent finger movement. In the absence of a significant parallel descending input to the motoneurons of distal muscles, voluntary activity of forearm muscles to allow functional grasp and release would also presumably be irretrievable. The fact that the stroke patients' ability to activate EDC as well as 1DI was clearly correlated with the presence of responses to TMS would corroborate this idea.

Other TMS and TES investigations of stroke patients have found that responses in hand muscles reappear when patients regain voluntary movement (Dominkus et al., 1990; Chu and Wu, 1992; Escudero et al., 1992; Heald et al., 1993a,b). Because of the interest in using evoked responses to TMS as a prognostic indicator, patients were first tested within a few days of stroke in these investigations. Cerebral oedema may have exacerbated the weakness so early after stroke and could also have affected the path of currents induced by TMS and any EMG responses. For this reason the late occurrence of responses and activity in hand muscles of the slowly recovering patients in my study was particularly interesting. They cannot be attributed to the dispersion of oedema or other transient disturbances in cell metabolism that occur in the early days after stroke.

What changes in the cortex might account for recovery of connectivity and function? PET studies of patients who have regained finger movement following capsular lesions, have demonstrated significant increases in rCBF in the motor cortex on both the

contralateral and ipsilateral sides, when the patients performed finger to thumb exercises with the recovered hand (Chollet et al. 1991; Weiller et al. 1993). Greater rCBF than normal was also found in variable combinations of the contralateral supplementary motor areas, insula, frontal and parietal cortex. In some patients a ventral extension of increased rCBF from the arm/hand area of the motor cortex into the face region, was associated with movement of the affected fingers (Weiller et al. 1993). These patients had little or no problem with the facial musculature after stroke, and had lesions that would have spared the part of the internal capsule (the genu) thought to carry descending cortico-bulbar fibres destined for the facial nucleus in the brainstem. Although it seems likely that cortical reorganisation contributes to recovered hand function after stroke, the connectivity from new representations of hand movement in the cortex to the effectors cannot be determined by PET. For example, the recovered hand movement in the patients studied by Weiller et al. (1993) may have been mediated by collaterals of cortico-bulbar fibres arising in the face area of the motor cortex and projecting indirectly via the facial motor nucleus or directly to the spinal cord, by CS fibres from the non-primary motor areas, or by ipsilaterally projecting fibres from the unaffected cortex (see Lemon 1993b). The changes in the presence and latency of responses to TMS that correlated with recovery at least suggest that the recovery is mediated by the lateral CST. In some patients response latencies reduced to normal during the recovery period, suggesting that changes in CS conduction, or in the time taken for temporal summation, were taking place rather than mediation by an alternative pathway. It is not possible to determine whether the appearance of these responses was due to excitation of CS fibres from areas other than motor cortex. Higher stimulus intensities are required to evoke muscle responses from other motor areas (see Hepp-Reymond, 1988). Mediation of EMG responses originating from cells in the supplementary motor area (SMA) cannot be discounted as recent evidence suggests there is a significant projection of CS fibres projecting from the SMA

to the motor nuclei of hand muscles (Rouiller et al., 1996). High thresholds were maintained in some patients despite recovery of hand function. This could be due to mediation of responses from the SMA, or it could simply reflect the reduction in intact CS fibres from the motor cortex. The lack of ipsilateral responses in the hand muscles of recovered patients suggests that the PET results showing increased rCBF seen in the undamaged hemisphere during the production of finger movement of the affected side was probably not indicative of an important mechanism for recovery of hand function.

7.3 Other descending motor pathways may contribute to the recovery of proximal upper limb movement.

Recovery of arm movement was often accompanied by responses in biceps and deltoid, however in contrast to the results for distal muscles, there were instances in the longitudinal study, in which patients demonstrated clear voluntary EMG, but no response to TMS. In normal subjects the contribution of CS input to the deltoid and biceps was confirmed as being relatively weaker than to the 1DI (see chapter 6). Subsequent investigation of the effect of voluntary activation of deltoid on responses to TMS on the affected and unaffected side in stroke patients gave some support to the idea that strengthening of other non-CS, descending inputs to the motoneurones of proximal muscles may be a mechanism for recovery of arm movement. Two of the three patients investigated showed smaller gains in response amplitude to TMS with increasing muscle contractions of the affected side than with equivalent activity on the unaffected side.

The most probable candidate for substituting some of the loss from CS inputs to motoneurones of proximal upper limb muscles is the reticulospinal tract. It is the only brainstem pathway that receives projections from the cortical motor areas and has widespread influence over the spinal cord (Kuypers, 1981, 1987). The reticulospinal tract originates primarily from the pons and the medulla and descends mainly ipsilaterally, but

terminates bilaterally in the ventral grey matter of the spinal cord, in part because some of the fibres cross over within the cord (Kuypers, 1981). Mediation via the reticulospinal tract might explain the presence of long latency ipsilateral responses in proximal muscles of both normal subjects and in patients. Ipsilateral responses were more easily evoked in the severely affected group of stroke patients. However, even in these patients ipsilateral responses were not abundant. In addition to disruption of CST, it is likely that these more severely affected patients also suffered greater damage to fibres projecting from the cortex to the brainstem than the patients in the less affected group. This may in part explain why ipsilateral responses from the damaged cortex were not common.

7.4 Implications for rehabilitation and future treatment of stroke patients.

The most important conclusion to be drawn from this study has been the confirmation that reorganisation of the CST originating from the damaged hemisphere is important for recovery of hand function after stroke. This finding has implications both for the development of Occupational Therapy programmes and also for the application of future brain repair treatments in stroke patients.

7.4.1 Implications for Occupational Therapy.

Reorganisation within the CNS must be subserved by some form of synaptic plasticity. The mechanisms underlying the recovery process may be similar to those that are responsible for learning (Carr and Shepherd, 1987ab). Enhanced synaptic transmission has been postulated as a mechanism for learning and memory processes. Synapses are strengthened when afferent fibres receive repetitive input, that leads to a response that is beneficial to the organism. If the input is insignificant, the opposite occurs and the synaptic strength of the presynaptic terminals are weakened. The repetitive input induces molecular changes in presynaptic and postsynaptic terminals which in turn change their effectiveness (see Kandel, 1991). Similarly the molecular changes that occur to change

the strength of synapses may also lead to an increase or decrease in the number of presynaptic terminals (Bailey and Chen, 1983). Most of the progress in the cellular study of learning has come from examining elementary forms of reflexive learning, e.g. sensitisation, habituation and classical conditioning in simple systems such as the marine snail, *Aplysia* (see Kandel, 1991), however a similar mechanism has been demonstrated in mammals. Long term potentiation (LTP) occurs after a brief high frequency train of stimuli to any one of three afferent pathways to the hippocampus (Bliss and Lømo, 1973). An increase in the excitatory synaptic potentials in the postsynaptic hippocampal neurons results, which can last for days or even weeks. LTP is thought to be a mechanism underlying associative and non-associative learning in man (Kandel and O'Dell, 1992; Grant, O'Dell, Karl, Stein et al., 1992). Changes in the motor cortex that are related to motor learning may also be brought about by LTP and the formation of new synapses (Greenough, Larson and Withers, 1985; Asanuma and Keller, 1991; see Halsband and Freund, 1993). It has been found that tetanic stimulation of the sensory cortex in cats produces LTP in the motor cortex (Sakamoto, Porter and Asanuma, 1987) and also that stimulation of the ventrolateral nucleus of the thalamus can also induce LTP in motor cortex, providing the sensory cortex is simultaneously stimulated (Iriki, Pavlides, Keller and Asanuma, 1989). If therapy was directed at repeatedly accessing the CS neurones and their connections remaining after stroke, then recovery of patients' hand function may be improved.

How can existing inputs be strengthened and new connections to remaining CS fibres be facilitated by Occupational Therapy? Many therapists, concerned that plastic changes at the spinal motoneurone level may be causing spasticity, concentrate their efforts on trying to manipulate spinal reflex pathways by providing afferent input through cutaneous or proprioceptive handling (Kidd et al., 1992). Their hope is that they can prevent any increase in the influence of facilitatory connections from the periphery that

might lead to hyperreflexia (see Goldberger and Murray, 1988) and so leave the motoneurone pool open to the influences of any remaining or recovering descending input (Kidd et al., 1992). A recent study demonstrated that this approach had at least an immediate effect on improving the CS input, accessible by TMS, to motoneurone pools serving extensor carpi radialis (a wrist extensor muscle), but the effect was markedly less than when patients attempted to activate the target muscle voluntarily (Hummelsheim, Hauptmann and Neumann, 1995). These results demonstrate the more powerful influence on motor cortex from areas upstream, that are responsible for internally generated movements, e.g. from the basal ganglia or from other cortical motor areas, in comparison with the relatively weaker effects of the proprioceptive and cutaneous inputs from popular therapeutic manouvres or handling techniques.

Rather than expecting patients to respond to rather indiscriminate manipulation by the therapist, connections to spared CS neurones after stroke may be potentiated more effectively if patients are encouraged to be more active in their therapy. Training programmes that require patients to perform actions or movements repeatedly with the affected hand have been shown to improve recovery of hand function in patients who already have a limited degree of movement (Turton and Fraser, 1990; Sunderland, Tinson, Bradley, Fletcher et al., 1992; Bütetfisch, Hummelshiem, Denzler and Mauritz, 1995). An obvious conclusion to draw from the apparent success of this strategy would be that patients should practice daily living tasks using the affected limb in order to improve its recovery. Unfortunately very often they don't. Severely affected patients find the affected limb impossible to use and those less severely affected often find it too slow, tiring and frustrating to use for everyday tasks. It is quicker and easier to use the unaffected hand. However extensive and long lasting improvement in motor function has resulted in patients, who having recovered a limited degree of hand and arm movement, have participated in a two week period of training in which the unaffected limb was restrained

during the daytime (Taub, Miller, Novack, Cook et al., 1993).

Tasks demanding high levels of temporal or spatial accuracy require even greater activity from cortical areas that project to the motor cortex (Grafton, Mazziotta, Woods and Phelps, 1992; Shibasaki, Sadato, Lyshkow, Yonekura et al., 1993). In normal adult subjects or intact monkeys, long lasting increases in body part representations in somatosensory and motor cortical areas accompany repeated participation in tasks requiring sensory discrimination or in learning a movement sequence (Karni et al., 1995; Pascual-Leone et al., 1995; Nudo, Milliken, Jenkins and Merzenich, 1996). The increase in sensory or motor body part representations are greater when the task places greater attentional demands on the subject (Recanzone, Merzenich, Jenkins, Grajski and Dinse, 1992; Pascual-Leone et al., 1995). Patients who cannot use the affected limb in many activities of daily living, but whose higher cognitive abilities are spared might be able to use these functions in their motor training. Tasks that rely especially on inputs to the motor cortex from other areas might be useful for building upon any residual movement that the patient has. For example, Lee, Lough and Lough, (1984) found that stroke patient reaching was smoother and faster when reaching to catch a ball that was rolling along a track, than when reaching to a stationary ball. A moving target provides a strong perceptual component to a reaching task, and presumably involves increased input to the motor cortex from the parietal cortex (Jeannerod, 1988). Similarly the properties of various objects to be picked up might promote flexibility in hand movements (Carr and Shepherd, 1987a). Their shape, weight and texture will determine the best grip to use and encourage changes in the balance of synergists that combine to form the grip. These strategies for increasing the repertoire of movements available to patients are currently employed by some therapists who base their clinical practice on motor skills acquisition research from sport and psychology fields (Carr and Shepherd, 1987ab; Turton and Fraser, 1990; Goodgold-Edwards, 1991). It would be exciting to find that these ideas were

substantiated by neurophysiological evidence showing that they were a sound and effective means of accessing spared CS fibres after stroke.

7.4.2 Implications for future brain repair treatments for stroke patients.

Even if the best therapeutic strategies were known and implemented, it is probable that many patients would still be left with significant disability after stroke. Those with large lesions, such as the more severely affected patients in the longitudinal study, may well have lost too much brain tissue to allow effective reorganisation. The outlook for such patients may improve with the development of brain repair treatments. CS axon regeneration resulting in recovered function has proved possible in lesioned rats treated with antibodies to neurite growth inhibitors (Bregman et al., 1995). Methods for the application of such treatments to humans are likely to be pioneered in the foreseeable future. The success of such developments depend on accurately targeting treatment to the areas of the CNS that will lead to the most beneficial effects. Much valuable evidence for the function of various descending systems has been obtained from animal work (see Porter and Lemon, 1993). The results of this study add to the body of scientific evidence that shows that the CST, originating in the contralateral hemisphere, is most important for hand function and that recovery after stroke is dependent upon reorganisation of the same CS system.

APPENDIX.

MEASUREMENT OF INDEPENDENT FINGER MOVEMENT AND MIRRORING USING ELECTROGONIOMETERS.

A1.1 Introduction.

Recovery of the capacity to perform skilled, independent finger movements may be viewed as a sign of the integrity of the CST after stroke. How should this be measured? The clinical tests of hand function used in this research, though useful, were affected by aspects of function other than the patient's finger movement, e.g. sensory impairment or poor proximal arm movement and strength. EMG records of patient's performance of different tasks can reveal some qualitative differences between the motor output of affected and unaffected hands (see chapter 3, section 3.3.2), but these would be difficult to quantify. A simple method for measuring the capacity to perform movement of individual digits was developed. The independence of index finger flexion and extension from movement of the middle finger of the same hand and from movement of the index finger of the contralateral hand (mirroring) was measured using electrogoniometers

A1.2 Method

A1.2.1 Subjects and patients.

Ten normal subjects aged between 40 and 74 years and five patients, aged 38-72 years were tested. All the patients had hemiparesis affecting the right preferred hand. Two of the patients, SO and FD had participated in the longitudinal study. SO was tested with the goniometers at nine months after stroke, FD was tested at four months and then again at twelve months. Both patients had small and late responses to TMS in the affected EDC

and 1DI when the damaged hemisphere was stimulated and no secure ipsilateral responses in these muscles.

A1.2.2 Tasks

The subject sat with both forearms in mid-pronation resting on a table in front of them. To start with all the fingers of both hands were resting with the metacarpophalangeal (MCP) and the interphalangeal (IP) joints slightly flexed (c.30°) in a relaxed position, the thumb was resting in mid position, in line with the forearm, so that the distance between finger and thumb tips was approximately 5 cm. The subject was then instructed to flex the index and middle fingers of one hand to meet the thumb, (an excursion of approximately 25° at the MCP and 45° at the proximal IP joints of both fingers) and then return them to the start position and to keep repeating the cycle at a comfortable self-paced speed. The ring and little fingers were to remain still, as in the start position. This easy task was performed to familiarise the subject with moving the fingers while wearing the goniometers and ensured that two or three complete cycles were visible in each 4 second sweep displayed on the computer screen. The subject was asked to maintain the start or rest position of the other hand throughout the task. Five sweeps were collected. During the task, the subject watched the moving fingers, rather than the computer screen. The subject was then asked to repeat the movement with the index finger only, without any middle finger movement. Again 5 sweeps were collected. These tasks were completed by each hand in turn.

Mirroring was tested by asking subject to move the index finger only again, as described above. The subject was asked first to move the preferred index finger (affected in patients), and keep the non-preferred index finger still (unaffected for patients). The procedure was repeated for intended movement of the non-preferred hand and the subject was reminded not to move the fingers of the contralateral hand. Five sweeps of data were collected for intended movement of each hand.

A1.2.3 Goniometers and their application.

Two electrogoniometers (Penny and Giles, type M65) were used. The goniometers consist of a 80 mm flexible steel strip which has been strain gauged. They are light (about 10 grams) and require little force to bend them: <5 gms (<0.5 N). The voltage output is linearly proportional to the angle subtended by one end relative to the other (Nicol, 1989). The small goniometer signals were amplified x390 and then captured via a 1401 interface, using CED SIGAVG software. Data was digitised at 100 Hz. Sweep length was 4 seconds.

To measure independence of index finger flexion /extension from movement of the middle finger of the same hand, the goniometers were attached to the index and middle finger of the each hand in turn. They were taped at each end to the distal phalange of the respective fingers and over the dorsum of the hand just distal to the wrist. Thus they spanned both the MCP and proximal IP joints of each finger. To measure the independence of index finger flexion /extension from movement of the index finger of the contralateral hand, a goniometer was attached to each index finger.

Because only two goniometers were available the independence of finger movement from middle finger movement of the same hand and the mirroring between hands had to be tested separately. The tasks were ordered for the minimal number of transferences of the goniometers:

1. Goniometers on preferred (affected) index and middle fingers: move two fingers, then index only.
2. Goniometers on index finger of each hand: move index only preferred, (affected in patients), then non-preferred (unaffected).
3. Goniometers on non-preferred (unaffected) index and middle finger: move two fingers, then index only.

A1.2.4 Analysis

The peak displacement displayed from each goniometer was measured from the second cycle of the second sweep for each condition, providing the subject had settled into a regular pattern of movement. In case of any irregularities a cycle from a subsequent sweep was selected. The amount of unwanted middle finger or homologous index finger flexion and extension that accompanied the index finger movement was calculated. Performance between hands in individual subjects was compared with a paired t-test (two tail) and patients unaffected side performance was compared with normal subjects non-preferred hand using non-related t-test, (two tail).

A1.3 Results

A1.3.1 Individual finger movement within hand.

Within the same hand, all subjects exhibited incomplete isolation of index finger movement. Some unwanted middle finger movement occurred during the "index finger only task" (see table A1.1). In normal subjects the middle finger movement ranged from 0% up to 54% of the index finger movement. There was no significant difference between the preferred and non-preferred hands. The mean was 21.7% for the preferred hand and 21.2% for the non-preferred hand. There was no correlation of the amount of extraneous middle finger movement with age.

When moving the index finger of the unaffected hand, the patients' middle fingers moved on average 23.3% of the range covered by the index finger. There was no significant difference between the performance of patients' unaffected hand and the normal subjects non-preferred hands. However when moving the index finger of the affected hand three of the patients were completely unable to isolate the index finger movement. Their middle fingers accompanied the index finger throughout the entire flexion and extension cycle.

Table A1.1 Goniometer assessment of individual finger movement.

Normal subjects			Within hand unwanted middle finger movement (as % index finger movement)		Between hands (mirroring) unwanted index finger movement in contralateral hand (as % voluntary ipsilateral index finger movement)	
Subject	age	handedness	preferred hand	non-preferred hand	mirroring in non-pref hand during mvt of preferred hand	mirroring in preferred hand during mvt of non-preferred hand
1	40	R	41	32	0	10
2	60	R	22	4	0	4
3	40	R	5	13	0	0
4	40	L	11	22	0	0
5	60	R	54	65	0	0
6	49	R	26	14	0	1
7	58	L	18	18	0	0
8	74	R	10	16	0	2
9	64	R	26	29	0	2
10	64	R	4	0	0	0
<hr/>						
Mean			21.7	21.2		
S.D.			16.0	18.3		
Patients					mirroring unaffected hand during mvt of affected hand	mirroring in affected hand during mvt of unaffected hand
age	hand affected	affected hand	unaffected hand			
SO	38	R	32	0	0	0
BC	54	R	16	55	7	0
FD	52	R	108	32	2	1
VP	73	R	129	25	1	0
GF	72	R	113	26	0	0
<hr/>						
Mean			79.6	27.6		
S.D.			51.7	19.6		

Significant difference for patient group, $t=2.01$, between within hand performance of affected and unaffected sides.

The performance of the remaining three were within the range of the normal subjects. Surprisingly, one patient had remarkably better control of the affected side than of the unaffected side.

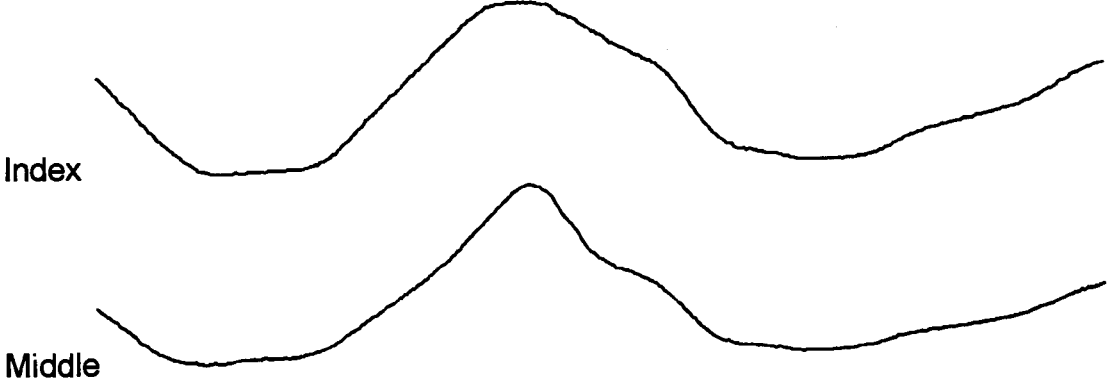
A1.3.2 Individual finger movement between hands.

The isolation of index finger movement between hands was much better. None of the normal subjects showed any detectable movement of the index finger on the non-preferred side when they were performing the task with the preferred hand. When intending to move the non-preferred index finger only, movement was detected in the preferred hand in five of the subjects. In three of them the mirrored movement was very slight. In most of the patients also there was little or no mirroring evident (see table A1.1).

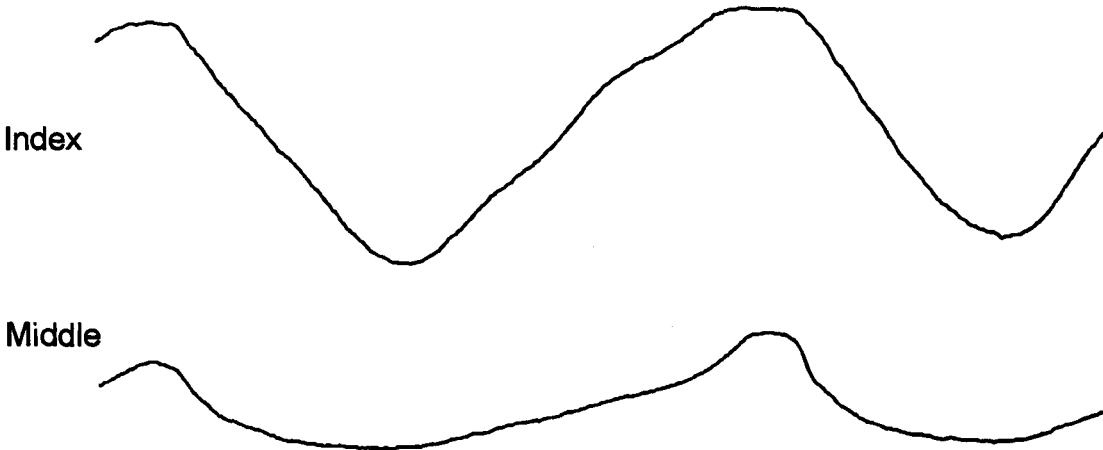
A1.3.3 Serial tests patient FD.

Patient FD's test results at four and twelve months after stroke are shown in table A1.2. At four months after stroke, Patient FD could complete the peg transfer test only with great difficulty, his affected hand took 70 seconds to move the ten pegs (unaffected hand took 10 seconds). The goniometer tests showed that he was able to flex and extend the fingers, but he was completely unable to prevent the middle finger from moving when he attempted to flex and extend the index finger in isolation. He displayed only slight mirroring in the unaffected hand when he performed the task with his affected hand. At twelve months, his hand function had improved, peg test time was 36 seconds with the affected hand. His individual finger movement within the affected hand was improved. The amount of unwanted middle finger movement was reduced to 55%. Mirroring by the unaffected hand when he attempted the task with the affected hand was minimal.

affected hand at 4 months



affected hand at 12 months



unaffected hand at 12 months

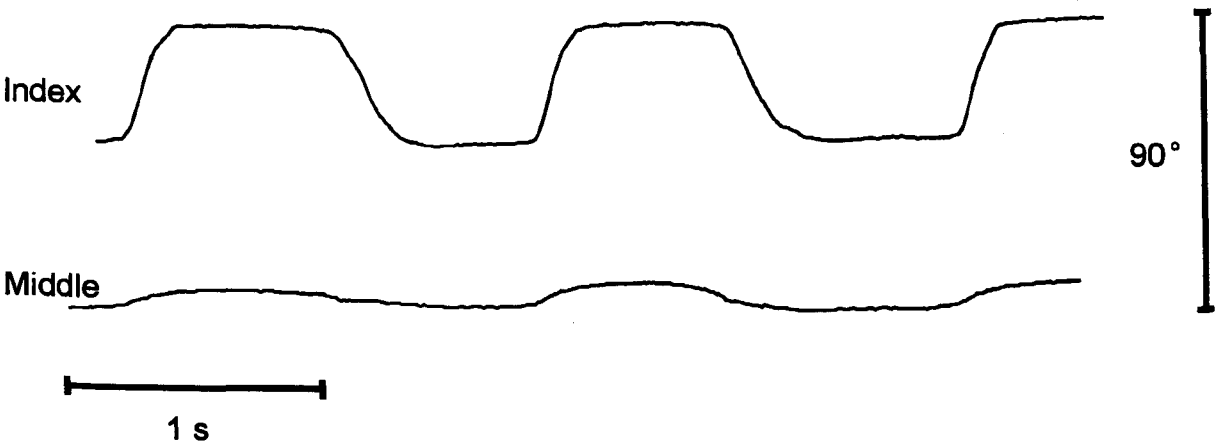


Figure A1.1 Patient FD individual finger movement

Performance of index finger flexion (down on trace) and extension (up). The amount of unwanted middle finger movement in the affected hand is less at 12 months than at 4 months. The performance of the unaffected hand at 12 months is shown for comparison. Note that the movement cycle takes longer with the affected hand and the amplitude is more exaggerated.

Table A1.2 Patient FD individual finger movements at 4 and 12 months after stroke.

Within hand		
unwanted middle finger movement (as % index finger movement)		
months after stroke	affected hand	unaffected hand
4	108	32
12	55	17

Between hands (mirroring)		
mirroring in unaffected hand during mvt of affected hand		
months after stroke	mirroring in affected hand during mvt of unaffected hand	
4	2	1
12	1	0

Note: Mirroring expressed as percentage of the voluntary movement performed by the opposite hand

A1.4 Discussion

A1.4.1 Control of individual finger movement within hand.

It is not surprising that complete independence of index finger movement was rarely achieved, even in normal subjects, since finger movement is mediated by systems that are organised for co-ordinated action of a group of digits rather than for separate control of each finger. At the muscular level, many of the extrinsic muscles that are primarily responsible for flexion and extension of the fingers are multitendoned and at the cortical level the majority of CM cells facilitate activity in a number of different hand muscles (Lemon, Bennett and Werner, 1991; see Porter and Lemon, 1993; Schieber and Hibbard, 1993; Kilbreath and Gandevia, 1994; Schieber, 1995). Proficient individual finger action depends on the skilled interplay between extrinsic and intrinsic muscles. Although both extrinsic and intrinsic muscles are normally be active in flexing and extending the fingers, the extrinsic muscles are the prime movers. The activation of intrinsic muscles is necessary for more fractionated movement since they act more selectively on the finger joints (Bejjani and Landsmeer, 1989) and achievement of individual finger movement may depend on the recruitment of intrinsic hand muscles to counteract unwanted muscle action (Darling, Cole and Miller, 1994; Schieber, 1995). It is probable that the stroke patients were able to move the fingers to the thumb under extrinsic control alone, but the inability to move the index finger on its own was probably due to poorer intrinsic muscle control in the stroke patients.

Although patient FD demonstrated better individual index finger movement within his affected hand at twelve months after stroke than he had at four months, the improvement was not accompanied by changes in responses characteristics that would support this idea. His response thresholds and latencies did not decrease and his response amplitudes did not increase in either EDC or 1DI.

A1.4.2 Control of individual finger movement between hands.

When moving the preferred index finger, none of the normal subjects mirrored the movement with the non-preferred index finger. When using the non-preferred hand some of them showed slight mirror movements in the other hand. There was little or no mirroring in most of the stroke patients. Although intense mirror movements are often seen in children (Connolly and Stratton, 1968), they are considered to be pathological in adults (Cohen, Meer, Tarkka, Bierner et al., 1991). Slight mirror movements (Liederman and Foley, 1986; Carr et al. 1993) and small amounts of mirror EMG activity in 1DI, have previously been found in normal adults (Mayston, Carter, Whybrow, Lockley et al., 1994). They are more apparent with increased effort (Todor and Lazarus, 1986) and more prevalent in the preferred hand, i.e. when the non-preferred hand is performing the intended movement.

In patients with congenital mirror movements, evidence for branched last order presynaptic inputs to the motoneurone pools of homologous muscles has been found (Farmer et al, 1990, Carr et al, 1993). It is not clear why mirrored EMG or slight movements occur in the contralateral hand of some normal subjects when performing independent finger movements with the non-preferred hand. No evidence for common input to homologous motoneurone pools has been found in normal subjects (Carr et al., 1993), though ipsilateral activation of motor cortex during finger movements has been found (Kawashima et al, 1993, 1994; Kim, Ashe, Hendrich, Ellermann et al., 1993). The evidence from functional magnetic resonance imaging suggests that there is asymmetry of ipsilateral motor cortex activation. Whereas the right motor cortex was activated mostly during contralateral finger movements in both right and left handed subjects, the left motor cortex was activated more substantially during ipsilateral movements, especially in right handed subjects (Kim et al, 1993). The lack of synchrony in motor unit firing between left and right muscles in normal subjects suggests that more indirect pathways

are responsible for the appearance of mirroring, one possibility is that they are the result of poor transcallosal suppression.

A1.4.3 Conclusion.

The electrogoniometer measurements were effective in demonstrating that normal subjects are not completely able to suppress the movement of additional fingers and that some stroke patients who have recovered some degree of hand function are even less able to do so. Further work is needed to establish the reliability of repeat testing. I was somewhat surprised to find that the stroke patients did not mirror to an extent that was greater than in normal subjects. Patients often mirror with the unaffected hand when they are trying to use the affected hand during occupational therapy. It seems that they are quite easily able to suppress mirrored movement if they are asked to keep the hand still.

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